ORIGINAL ARTICLE

# Pharmacological Treatment of Glaucoma and Biomechanical Properties of the Cornea

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## SUMMARY

**Purpose:** To evaluate and compare the impact of the long-term use of medication to reduce intraocular pressure on the biomechanical properties of the cornea.
**Material and methods:** A study sample of 305 eyes of 154 patients newly diagnosed with primary open angle glaucoma (POAG, n = 68) or ocular hypertension (OH, n = 6) was included in a prospective cohort study. The control group comprised 80 untreated eyes of 40 patients with ocular hypertension and 80 eyes of 40 patients with no ocular pathology. The following parameters were evaluated: intraocular pressure (IOPg, IOPcc), hysteresis (CH), corneal resistance factor (CRF) and central corneal thickness (CCT). The parameters were evaluated at baseline (untreated) and at follow-up intervals of 3, 6, 9 and 12 months. The same schedule was used for the eyes in the control group. Eyes with POAG or OH were divided into two sub-groups, depending on the type of applied medication: prostaglandin analogues, carboanhydrase inhibitors alone or in combination with beta-blockers.
**Results:** We did not demonstrate any statistically significant difference in hysteresis in patients with newly diagnosed POAG (as yet untreated) in comparison with the normal eyes in the control group ($p = 0.238$). We demonstrated significantly higher values of CRF ($p = 0.032$) and CCT ($p = 0.013$) in the control group of untreated patients with ocular hypertension. This result confirms a higher number of patients with stiffer and thicker corneas. A statistically significant difference of CH and CRF was demonstrated ($p < 0.0001$) in eyes treated by prostaglandin analogues during the follow up period. In these eyes we also demonstrated a reduction of CCT ($p < 0.001$). We did not record any other statistically significant change in the remaining observed parameters.
**Conclusion:** The increase in CH and CRF may demonstrate a change of the biomechanical properties of the cornea following the long-term use of prostaglandin analogues. The biomechanical properties of the cornea were not impacted upon by carboanhydrase inhibitors. Further studies are required in order to establish the effect of the long-term use of prostaglandin analogues on the accuracy of IOP measurements.

**Key words: glaucoma, intraocular pressure, cornea, hysteresis, central corneal thickness**

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## INTRODUCTION

The biomechanical properties of the cornea – elasticity and viscosity influence the physiological and pathophysiological functions of the cornea. They determine how the corneal tissue shall react to stress or change of shape.
The possibility of measuring biomechanical properties in vivo remains an important aim for certain diagnostic and therapeutic procedures in ophthalmology. At present the biomechanics of the cornea can be measured in clinical practice using an Ocular Response Analyzer (ORA) instrument. The ORA is a noncontact tonometer, which measures intraocular pressure (IOP) independently of central corneal thickness. It also provides parameters which represent the biomechanics of the cornea: Corneal Hysteresis (CH) and Corneal Resistance Factor (CRF). In refractive surgery it is possible to use this method in order to distinguish potential candidates in whom there is a risk of corneal ectasia following LASIK (1), and also to obtain a more precise diagnosis of certain corneal diseases (keratoconus, Fuchs endothelial dystrophy) (2-4).
In the case of primary open-angle glaucoma, a certain pathological link between viscoelasticity and glaucoma is also being considered. In patients with glaucoma, it is conclusively demonstrated that the cornea (5) and sclera (6, 7) have altered biomechanical properties. If intraocular pressure increases, greater stress is placed on these structures. If we consider that we are measuring a thinner and flexible cornea, this could testify also to a thinner and flexible lamina cribrosa. In the region of the lamina cribrosa, axons of the ganglion cells pass from the environment of the inside of the eye, where there is relatively higher pressure, into the environment of the retrobulbar cerebrospinal space, where the pressure is lower. The viscosity and elasticity of the lamina cribrosa is important for balancing the pressure gradient and providing functional support for the axons of the ganglion

cells, in order to prevent an interruption of the axoplasmic flow (8).
The variability of viscoelasticity may also influence the results of measurement of intraocular pressure.
From the perspective of assessment of the efficacy of treatment and compensation of intraocular pressure in complicated cases of patients with glaucoma, it is also important to obtain the most precise possible values.
We have been stimulated to compile this study by the as yet not entirely clarified issue of the possible connection between changes in the biomechanical properties of the cornea during the course of treatment with various types of antiglaucomatous drugs. Pharmacotherapy of glaucoma is represented by six main groups of pharmaceuticals, but only carboanhydrase inhibitors and prostaglandin analogues can potentially influence the structure of the cornea. Prostaglandin analogues activate the group of enzymes known as the matrix metalloproteinase (MMP), which are also present in the corneal stroma and may have an influence on the structure of collagen (9, 10). In general they are responsible for the degradation of the extracellular matrix (ECM). Inhibitors of carbonic anhydrase (ICA) may negatively influence the endothelial pump of the cornea (11) by inhibiting the enzyme carbonic anhydrase II, which is present in the cornea and shares in the optimal hydration of the cornea.

## METHOD

The prospective cohort study incorporated a study sample of 305 eyes of 154 patients.
The patients with newly diagnosed primary open-angle glaucoma (POAG) and ocular hypertension (OH) were compared with a control group. The control group comprised 80 eyes of 40 patients with ocular hypertension without therapy and 80 eyes of 40 individuals with no ocular pathology.
The patients with newly diagnosed glaucoma or ocular hypertension were included in the study if the clinical finding required the application of treatment to reduce intraocular pressure and they had not yet received treatment.
The elimination criteria for all groups were previous intraocular surgery, laser or surgical treatment of the cornea, degenerative, dystrophic or inflammatory disease of the cornea. Also eliminated from the study were patients who wore contact lenses, patients with a toric refractive error higher than 2 dioptres, patients who apply eye drops over the long term to reduce intraocular pressure, or who apply artificial tears or other anti-inflammatory drugs.

The study sample is composed of three groups.
*Group A* (n = 74) comprises patients with newly diagnosed POAG (n = 68) and OH (n = 6), in whom therapy was newly applied. 44 women (59.5%) and 30 men (40.5%) were included in the group. The average age at the time of determination of the diagnosis was 62.2 years in women (±10.36), in men 58.5 years (±11.61). In this group patients were divided into two sub-groups, A1 and A2. Sub-group A1 was treated with prostaglandin analogues (n = 45), A2 with carboanhydrase inhibitors separately (n = 12) or in a fixed combination with beta-blockers (n = 17).
*Group B* (n = 40) comprises patients with ocular hypertension in whom therapy was not required. The group included 21 women (52.5%) and 19 men (47.5%). The average age was 54.4 years in women (±12.5) and 53.5 years (±12.4) in men. Group C (n = 40) comprises healthy individuals with no ocular pathology. Group C included 26 women (65.8%) and 14 men (34.2%). The average age was 57.96 years in women (±12.15) and 52.14 years (±12.61) in men. The patients were assessed following inclusion in the study within a schedule of follow-up visits at an interval of 3, 6, 9 and 12 months. At the initial examination a personal and ocular anamnesis was taken and a complex ophthalmological examination performed. This concerned automated keratometry and refractometry (Nidek ARK-700A), determination of best corrected visual acuity (BCVA) for distance vision (ETDRS optotype table), determination of subjective manifest refraction (spherical composition and astigmatism), biomicroscopic examination of the anterior segment of the eye on a slit lamp, measurement of intraocular pressure using a noncontact ORA tonometer, measurement of corneal thickness using ultrasonic pachymetry (ORA), examination of the angle of the anterior chamber (Zeiss gonioscopic lens), examination of the fundus by indirect ophthalmoscopy with assessment of the C/D ratio on the disc of the optic nerve and examination of the field of vision (Humphrey – Zeiss perimeter).
The resulting curve of measurement of intraocular pressure, hysteresis and corneal resistance using an ocular response analyzer (ORA) were selected according to the quality score. The average was always taken of the values of the four best quality measurements. Similarly, ultrasonic pachymetry was the result of the average of the values of four measurements. The examination of the visual field was conducted after 6 months on the patients with glaucoma and ocular hypertension, in the control group of healthy individuals at the initial and final examination. The results of the measurement of the biomechanical properties of the cornea and intraocular pressure were evaluated statistically by means of a statistical analysis in the temporal development of the individual measured quantities IOPg, IOPcc, CH, CRF, CCT, by the method of correlation analysis and an ANOVA test.

## RESULTS

**Intraocular pressure IOPg and IOPcc** before the commencement of treatment and after 12 months of observation in group A, newly diagnosed and treated POAG and OH, in control groups B and C without treatment, is summarised in tables 1 and 2.
In sub-group A1, 87 eyes were treated with prostaglandin analogues, in the first year the number of observed eyes dropped to 73 (84%). The average value of intraocular pressure IOPg was 21.88 mmHg (±7.7 mmHg) at baseline before the application of treatment, with a maximum IOP value of 56.5 mmHg and minimum value of 16.7 mmHg. The corrected value of intraocular pressure IOPcc did not differ markedly. The average IOPcc value was 22.0 mmHg (±7.2 mmHg), with a maximum IOP value of 43.5 mmHg and minimum value of 16.3 mmHg. The average value of intraocular pressure IOPg at the end of the observed period was 17.6 mmHg (±4.5 mmHg) and IOPcc 19.0 mmHg (±5.8 mmHg). Intraocular pressure IOPg decreased by 4.2 mmHg and IOPcc by 3.0 mmHg in the observed period. Both values of IOPg and IOPcc show a falling trend.
In sub-group A2, 58 eyes were treated with carboanhydrase inhibitors separately or in a fixed combination with beta blockers, in the first year the number of observed eyes dropped to 48 (83%). The average value of intraocular pressure IOPg was 21.7 mmHg

**Table 1** Development of intraocular pressure IOPg in groups A1, A2, B and C

| IOPg | A1 – 1D | 12M | A2 – 1D | 12M | B – 1D | 12M | C – 1D | 12M |
|---|---|---|---|---|---|---|---|---|
| Min. | 16.7 | 10.5 | 17.7 | 10.1 | 21.7 | 15.7 | 10.1 | 10 |
| Max. | 56.5 | 27.9 | 50.4 | 31.2 | 40.8 | 31.3 | 26.9 | 22.4 |
| Median | 20.8 | 17.1 | 20.9 | 17.7 | 25.5 | 21.6 | 17.4 | 15.9 |
| Average | 21.8 | 17.6 | 21.7 | 18.5 | 26.4 | 21.7 | 17.4 | 15.6 |
| SD | 7.7 | 4.5 | 6.9 | 5.4 | 4.7 | 4 | 3.8 | 3 |
| Number | 87 | 73 | 58 | 48 | 80 | 61 | 80 | 72 |

IOPg = intraocular pressure equivalent according to Goldmann, A1 = group of POAG or OH treated with prostaglandin analogues, A2 = group of POAG or OH treated with ICA or ICA and beta blockers, B = group of ocular hypertension without treatment, C = control group
SD = standard deviation, 1D = 1st day, 12M = 12th month

**Table 2** Development of intraocular pressure IOPcc in groups A1, A2, B and C

| IOPg | A1 – 1D | 12M | A2 – 1D | 12M | B – 1D | 12M | C – 1D | 12M |
|---|---|---|---|---|---|---|---|---|
| Min. | 16.3 | 10.5 | 16.5 | 9.6 | 21.3 | 10.8 | 10.8 | 12 |
| Max. | 43.5 | 27.9 | 49.3 | 34.3 | 41.5 | 22.1 | 29.8 | 24.6 |
| Median | 20.8 | 17.1 | 20.6 | 18 | 22.9 | 19.7 | 17.8 | 15.5 |
| Average | 22 | 19 | 21.7 | 18.7 | 24.7 | 18.6 | 17.5 | 15.6 |
| SD | 7.2 | 5.8 | 7.2 | 5.3 | 4.2 | 3.2 | 4.3 | 3.4 |
| Number | 87 | 73 | 58 | 48 | 80 | 61 | 80 | 72 |

IOPcc = intraocular pressure compensated by properties of cornea, A1 = group of POAG or OH treated with prostaglandin analogues, A2 = group of POAG or OH treated with ICA or ICA and beta blockers, B = group of ocular hypertension without treatment, C = control group
SD = standard deviation, 1D = 1st day, 12M = 12th month

(±6.9 mmHg) at baseline before the application of treatment, with a maximum IOP value of 50.4 mmHg and minimum value of 17.7 mmHg. The average corrected value of intraocular pressure IOPcc was also 21.7 mmHg (±7.2 mmHg), with a maximum IOP value of 49.3 mmHg and minimum value of 16.5 mmHg. The average value of intraocular pressure IOPg at the end of the observed period was 18.5 mmHg (±5.4 mmHg) and IOPcc 18.7 mmHg (±5.3 mmHg). Intraocular pressure IOPg decreased by 3.2 mmHg and IOPcc by 3.0 mmHg in the observed period. Both values of IOPg and IOPcc show a falling trend.

In group B, 80 eyes with ocular hypertension remained untreated, the number of observed eyes dropped in the first year to 61 (76%). The average value of intraocular pressure IOPg was 26.4 mmHg (±4.7 mmHg) at the beginning of observation, with a maximum IOP value of 40.8 mmHg and minimum value of 21.7 mmHg. The average corrected value of intraocular pressure IOPcc was 24.7 mmHg (±4.2 mmHg), with a maximum IOP value of 41.55 mmHg and minimum value of 21.3 mmHg. The average value of intraocular pressure IOPg at the end of the observed period was 21.7 mmHg (±4.0 mmHg) and IOPcc 18.6 mmHg (±3.2 mmHg). Both values of IOPg and IOPcc remained above average over the observed period.

In group C, 80 eyes had no ocular pathology, in the first year the number dropped to 72 (90%). The average value of intraocular pressure IOPg was 17.4 mmHg (±3.8 mmHg) at the beginning of observation, with a maximum IOP value of 21.9 mmHg and minimum value of 10.1 mmHg. The average corrected value of intraocular pressure IOPcc was 17.5 mmHg (±4.3 mmHg), with a maximum IOP value of 22.1 mmHg and minimum value of 10.8 mmHg. The average value of intraocular pressure IOPg at the end of the observed period was 15.6 mmHg (±3.0 mmHg) and IOPcc 15.6 mmHg (±3.4 mmHg). The difference in the values of intraocular pressure IOPg and IOPcc over the observed period was minimal.

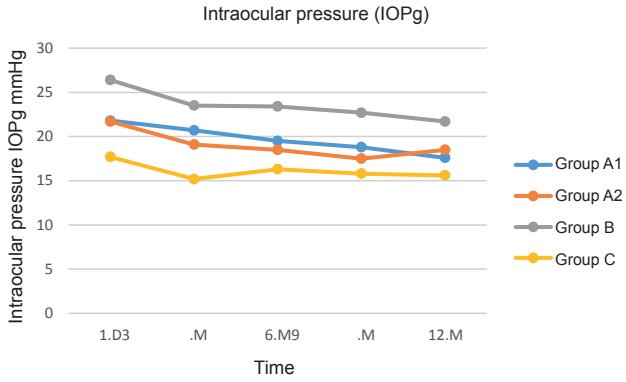
Corneal hysteresis (CH) and corneal resistance factor (CRF) before the commencement of treatment and after 12 months of observation in group A, newly diagnosed and treated POAG and OH, in control groups B and C without treatment, is summarised in tables 3 and 4.

In sub-group A1, the average value of CH was 10.5 mmHg (±2.2 mmHg) at baseline before the application of treatment, and at the end of the observed period 12.8 mmHg (±2.0 mmHg). The increase of the average value of CH was by 2.3 mmHg. The average value of CRF at the beginning of treatment was 11.7 mmHg (±2.2 mmHg) and at the end of the observed period 13.7 mmHg (±1.9 mmHg). The increase in the average value of CRF was by 2.0 mmHg.

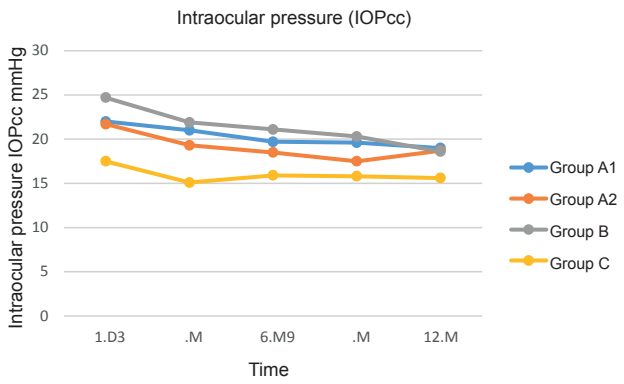
In sub-group A2, the average value of CH was 10.0 mmHg (±2.4 mmHg) at baseline before the application of treatment, and at the end of the observed period 10.2 mmHg (±2.2 mmHg). The average value of CRF at the beginning of treatment was 11.9 mmHg (±2.4 mmHg) and at the end of the observed period 11.1 mmHg (±2.5 mmHg). The difference of the CH and CRF values was minimal.

In group B, the average value of CH was 11 mmHg (±2.7 mmHg) at the beginning of observation, and at the end of the observed period 12.8 mmHg (±3.1 mmHg). The average value of CRF at the beginning of treatment was 14.2 mmHg (±3.0 mmHg) and at the end of the observed period 14.4 mmHg (±3.4 mmHg). The increase in the average value of CH was by 1.8 mmHg, the difference in CRF was minimal.

In group C the average value of CH was 10.5 mmHg (±2.0 mmHg) at the beginning of observation, and at the end of the observed period 10.8 mmHg (±2.0 mmHg). The average




**Graph 1** Temporal curve of IOPg in groups A1, A2, B and C.




**Graph 2** Temporal curve of IOPcc in groups A1, A2, B and C.

**Table 3** Development of CH in groups A1, A2, B and C

| CH | A1 – 1D | 12M | A2 – 1D | 12M | B – 1D | 12M | C – 1D | 12M |
|---|---|---|---|---|---|---|---|---|
| Min. | 6.3 | 7 | 5.5 | 4.6 | 6 | 8.6 | 5.2 | 6.7 |
| Max. | 16.2 | 17.2 | 17.6 | 15 | 18.1 | 20.3 | 14.6 | 14.5 |
| Median | 10.3 | 12.5 | 9.6 | 10.4 | 11 | 12.2 | 10.9 | 10.5 |
| Average | 10.5 | 12.5 | 10 | 10.2 | 11 | 12.8 | 10.5 | 10.8 |
| SD | 2.2 | 2 | 2.4 | 2.2 | 2.7 | 3.1 | 2 | 2 |
| Number | 87 | 73 | 58 | 48 | 80 | 61 | 80 | 72 |

CH = hysteresis, A1 = group of POAG or OH treated with prostaglandin analogues, A2 = group of POAG or OH treated with ICA or ICA and beta blockers, B = group of ocular hypertension without treatment, C = control group
SD = standard deviation, 1D = 1st day, 12M = 12th month

**Table 4** Development of CRF in groups A1, A2, B and C

| CRF | A1 – 1D | 12M | A2 – 1D | 12M | B – 1D | 12M | C – 1D | 12M |
|---|---|---|---|---|---|---|---|---|
| Min. | 6.8 | 8.9 | 7 | 6.1 | 9.7 | 9.9 | 6.7 | 5.9 |
| Max. | 17.4q | 17.9 | 18.6 | 17.1 | 22.1 | 22.3 | 14.6 | 15.2 |
| Median | 12 | 13.9 | 11.5 | 10.9 | 14.2 | 14.2 | 11 | 10.6 |
| Average | 11.7 | 13.7 | 11.9 | 11.1 | 14.2 | 14.4 | 11 | 10.8 |
| SD | 2.2 | 1.9 | 2.4 | 2.5 | 3 | 3.4 | 1.9 | 1.9 |
| Number | 87 | 73 | 58 | 48 | 80 | 61 | 80 | 72 |

CRF = corneal resistance factor, A1 = group of POAG or OH treated with prostaglandin analogues, A2 = group of POAG or OH treated with ICA or ICA and beta blockers, B = group of ocular hypertension without treatment, C = control group
SD = standard deviation, 1D = 1st day, 12M = 12th month

value of CRF at the beginning of treatment was 11 mmHg (±1.9 mmHg) and at the end of the observed period 10.8 mmHg (±1.9 mmHg). The difference in the values of CH and CRF was minimal.

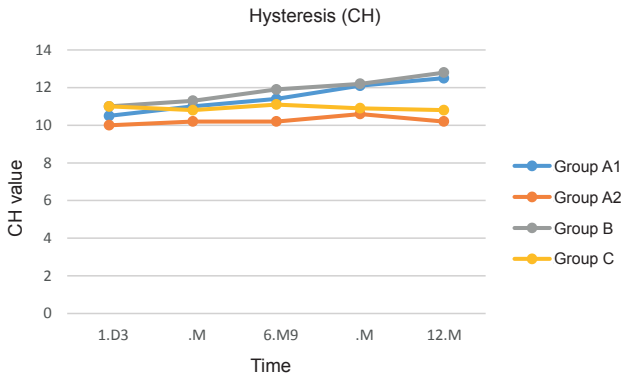
The resulting temporal curves of CH and CRF are documented by graphs 3 and 4.

Central corneal thickness (CCT) before the commencement of treatment and after 12 months of observation in group A, newly diagnosed and treated POAG and OH, and in control groups B and C without treatment, is summarised in table 5 and graph 5.

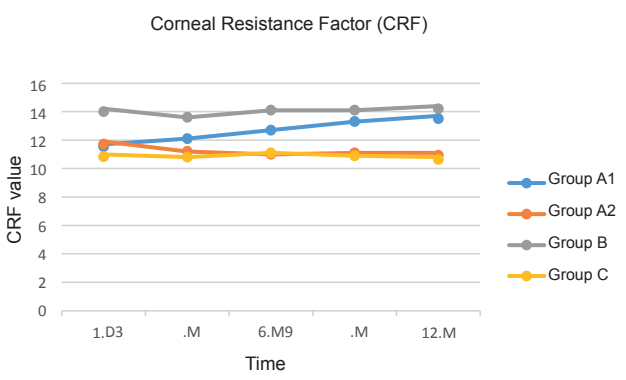
In group A1 the average value of CCT dropped over the course of the observation period by -18.8 µm. The increase in the average value of CCT in group A2 was by 14 µm. Control groups B and C manifested minimal differences.

The correlation analysis did not demonstrate a correlation between the quantities IOPcc, IOPg with CH and CRF in any of the groups either at baseline or after one year of observation. The Kruskal-Wallis non-parametric ANOVA (SW STATISTICA) method was used to test the differences between the groups for the quantities IOPg, IOPcc, CH, CRF and CCT at baseline and after 12 months. The test was conducted for the differential quantity after one year as against the baseline value.

Significant differences were demonstrated for the quantity IOPg at baseline between groups A1, A2, B and C ($p < 0.0001$). The differences can be seen from graph 6. The greatest variability of IOPg values is in group A1, whilst in comparison with the other groups, the lowest median is in group C, which confirms the average values of IOP in healthy individuals. Significant differences were demonstrated between groups A1, A2, B and C were also demonstrated for the quantity IOPcc on a 1% level of significance ($p = 0.0001$), analogous to the differences in quantity IOPg. According to graph 7, no significant difference was determined in the




**Graph 3** Temporal curve of CH in groups A1, A2, B and C.




**Graph 4** Temporal curve of CRF in groups A1, A2, B and C.

**Table 5 Development of CCT in groups A1, A2, B and C**

| CCT | A1 – 1D | 12M | A2 – 1D | 12M | B – 1D | 12M | C – 1D | 12M |
|---|---|---|---|---|---|---|---|---|
| Min. | 470 | 452 | 505 | 509 | 522 | 523 | 470 | 475 |
| Max. | 614 | 590 | 625 | 635 | 685 | 685 | 664 | 652 |
| Median | 556 | 539 | 553.5 | 570.5 | 607 | 604 | 568.5 | 564 |
| Average | 557 | 538.2 | 562 | 576 | 604.2 | 601.6 | 568.8 | 565 |
| SD | 32.4 | 31.2 | 31.7 | 29.7 | 39.1 | 40.7 | 39.1 | 36.7 |
| Number | 87 | 73 | 58 | 48 | 80 | 61 | 80 | 72 |

CCT = central corneal thickness, A1 = group of POAG or OH treated with prostaglandin analogues, A2 = group of POAG or OH treated with ICA or ICA and beta blockers, B = group of ocular hypertension without treatment, C = control group
SD = standard deviation, 1D = 1st day, 12M = 12th month

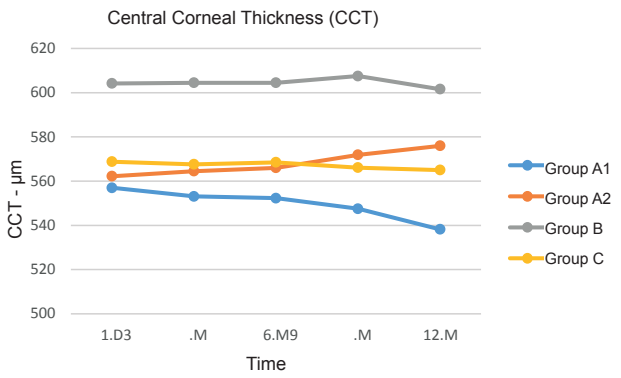
change in intraocular pressure for the quantity IOPg between groups A1, A2, B and C, in comparison with the baseline measurement (p = 0.6717). In the majority of patients the inter-year change of IOPg was small, whether it concerned an increase or decrease. A similar conclusion can be formulated also for the quantity IOPcc (p = 0.503), as illustrated by graphs 8 and 9.

No significant differences were demonstrated for the quantity CH at baseline between groups A1, A2, B and C (p = 0.3559). After one year a significant difference was determined in the change of hysteresis between the groups (p < 0.001), group A1 differs markedly – it has the highest median value. This means that in group A1 there was an increase of CH, an increase is also indicated by group B, but in a smaller number of eyes. In the remaining groups A2 and C, the CH value after one year is approximately the same as at the baseline measurement. The difference in the changes is documented by graphs 10 and 11.

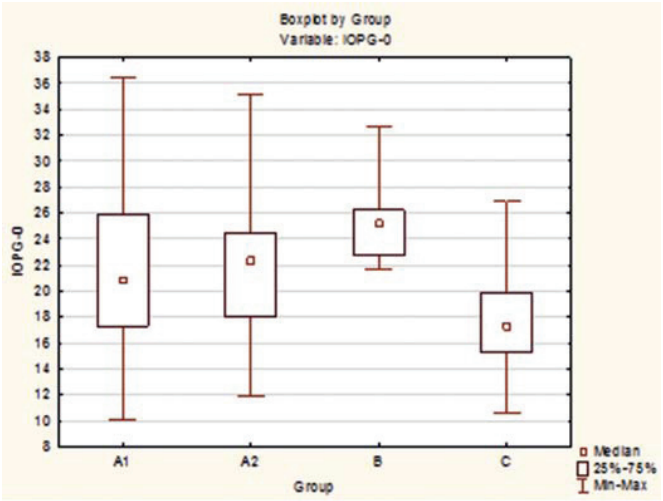
Significant differences were demonstrated for the quantity CRF at baseline between groups A1, A2, B and C (p = 0.032). According to graph 12, group B above all manifests different behaviour, acquiring generally higher values than the remaining three groups, which are mutually comparable. Also after one year a significant difference was determined between the groups in comparison with the baseline measurement on a 1% level of significance (p < 0.001), as documented by graph 13. Group A1 differs markedly, manifesting the smallest variability of change of CRF, and analogously with the case of CH it has the highest median value. In group A1 there was an increase of CRF, whereas in the remaining groups A2, B and C, the CRF value after one year is approximately the same as at the baseline measurement.

Significant differences were demonstrated for the quantity CCT at baseline between groups A1, A2, B and C (p = 0.0132). The greatest variability of CCT values is in group C, group B has a markedly higher median (above the level of 600 µm). After one year a significant difference was determined for the quantity CCT between groups A1, A2, B and C in the change of central corneal thickness in comparison with the baseline measurement on a 1% level of significance (p < 0.001). The differences are illustrated by graphs 14 and 15.

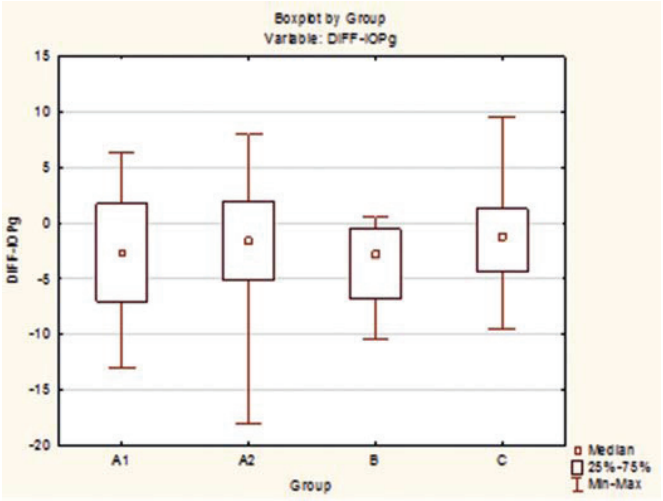
In group A1 the median is negative – in this group there was therefore a reduction in the CCT values after



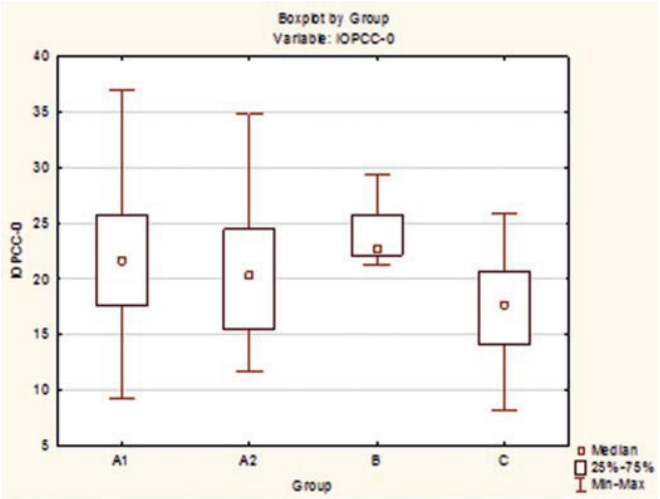

**Graph 5** Temporal curve of CCT in groups A1, A2, B and C.



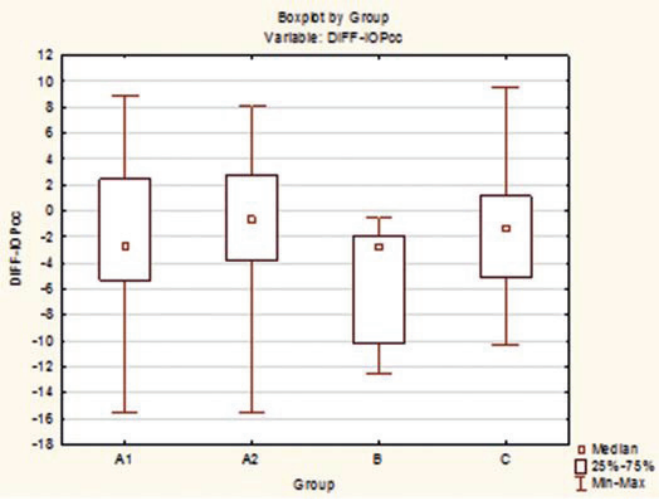

**Graph 6** Differences between groups A1, A2, B and C for quantity IOPg at baseline.



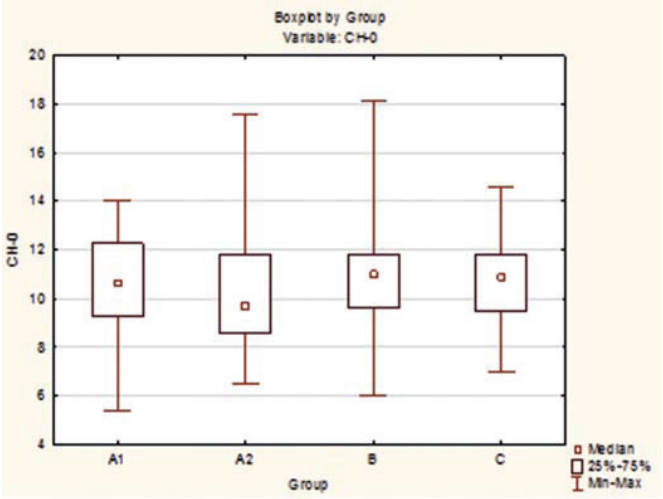

**Graph 7** Differences between groups A1, A2, B and C for quantity IOPg after 12 months.



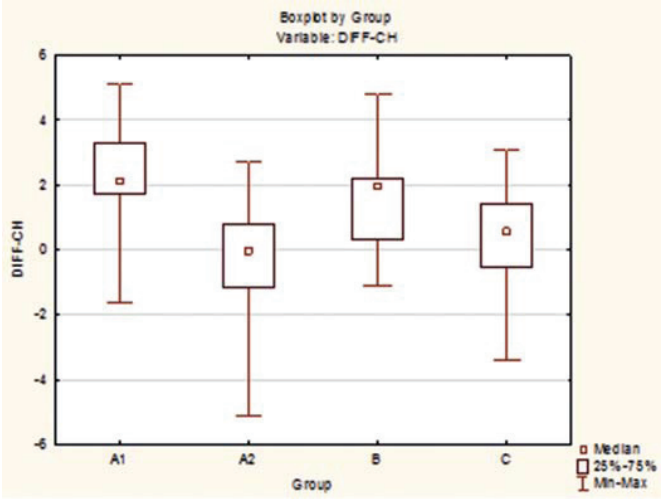

**Graph 8** Differences between groups A1, A2, B and C for quantity IOPcc at baseline.



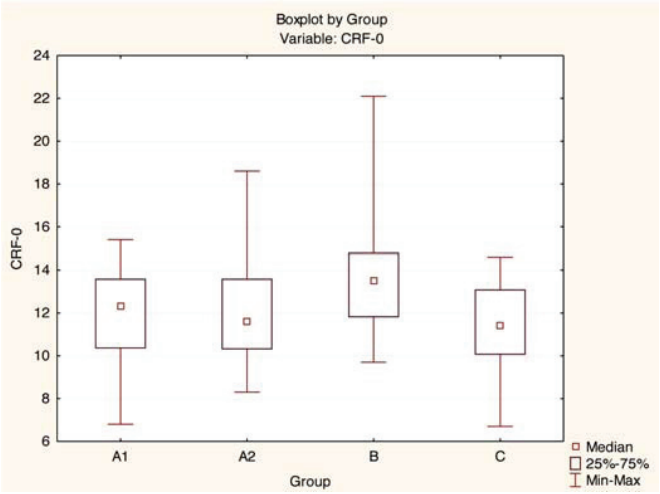

**Graph 9** Differences between groups A1, A2, B and C for quantity IOPcc after 12 months.



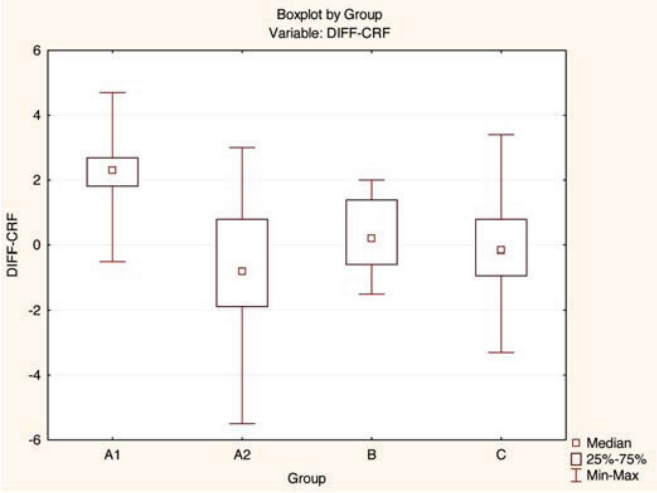

**Graph 10** Differences between groups A1, A2, B and C for quantity CH at baseline.



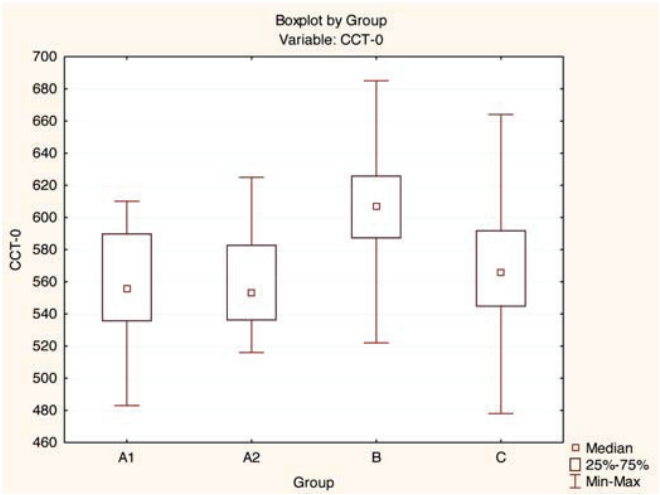

**Graph 11** Differences between groups A1, A2, B and C for quantity CH after 12 months.



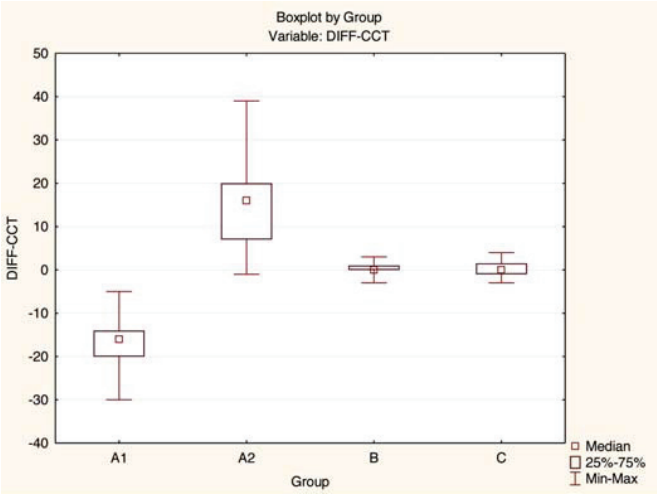

**Graph 12** Differences between groups A1, A2, B and C for quantity CRF at baseline.




**Graph 13** Differences between groups A1, A2, B and C for quantity CRF after 12 months.




**Graph 14** Differences between groups A1, A2, B and C for quantity CCT at baseline.




**Graph 15** Differences between groups A1, A2, B and C for quantity CCT after 12 months.

one year (by 5 μm, but also by up to 30 μm). A reduction was recorded in all the patients from this group. The median is 15 μm, which means that in half of the patients the reduction was larger or smaller than 15 μm. By contrast, in group A2 the median is positive – in this group there was therefore an increase in the CCT value after one year. A reduction was recorded in the majority of the patients from this group. On the other hand, this group had the greatest variability of inter-year change in CCT determined in individual patients. Groups B and C are comparable: in both there is very low variability and the median of this differential quantity and the median of this differential quantity is approximately zero in both groups. After one year, CCT in these groups was approximately the same as at baseline.

## DISCUSSION

Long-term pharmacotherapy of glaucoma has a favourable influence on the level of intraocular pressure, however, on the other hand it may be accompanied by a whole range of negative effects. The target area of the drugs which lead to a reduction of IOP is the corpus ciliare and the biochemical processes of its enzymes. With regard to the fact that a range of enzymes of the corpus ciliare are present also in the corneal stroma, some of these may also influence biochemical processes in the cornea. This has led to monitoring of the potential negative effects of pharmaceuticals which reduce intraocular pressure on the morphological, metabolic and biomechanical properties of the cornea.

Clinical manifestations of damage to the surface of the conjunctiva and cornea have been known for the greatest length of time in the group of beta blockers. Mietz et al. (12) demonstrated a significant increase in the subepithelial thickness of the collagen band of the conjunctiva in rabbits after 18 months of application of timolol. The negative effect is caused by the active agent of the beta blocker itself, and a toxic effect of the preservative agent was also confirmed.

The most frequently used preservative agent is benzalkonium chloride (BAC). Long-term stress on the surface of the eyes by benzalkonium chloride deteriorates the quality of the lacrimal film, reduces its stability and creates a hydrophobic environment of the surface of the eye. BAC also has toxic effects on the epithelial cells of the cornea and conjunctiva, breaches the haemato--ocular barrier and may be the cause

of allergic reaction. A range of studies also compare the effect of beta blockers on the surface of the eyes with and without the preservative agent BAC. The result is more favourable in favour of pharmaceuticals without BAC or with a low concentration thereof (13, 14). Beta blockers and BAC alter the morphology of the corneal epithelium, and do not have an influence on CCT and the biomechanical properties of the cornea.

Carboanhydrase inhibitors are another group of pharmaceuticals which can influence the structure of the cornea. The carbonic anhydrase enzyme in the eyes catalyses the chemical reaction of conversion of carbon dioxide and water into carbonic acid and vice versa. Isoenzyme II, which is important for the dehydration of the stroma, is present in the cornea. The activity of isoenzyme II may be blocked by ICA, which may result in edema and threat to the transparency of the cornea. A number of published studies in the area of this issue confirm the influence of ICAs on central corneal thickness (11, 15-18).

Wirtitsch et al. (16) in their randomised, placebo-controlled, double-blind trial confirmed a statistically significant increase in central corneal thickness after four weeks of application of dorzolamide in patients with Fuchs endothelial dystrophy in the phase of cornea guttata and unchanged central corneal thickness in healthy individuals.

Zhao and co-author (17) referred to two cases of patients in whom decompensation of the cornea occurred after treatment with brinzolamide, in one patient after fifteen months of treatment and in the second after 2 years. A mild edema appeared on the corneas, as well as greying of the stroma, it is of interest that central corneal thickness was unchanged. After discontinuation of treatment the finding disappeared within 3 months.

March et al. (18) published a randomised, double-blind trial in which 372 patients with primary glaucoma were treated with ICAs or beta blockers. After 18 months of treatment they did not demonstrate any changes in central corneal thickness or in the density of the endothelial cells. Similarly, Lester et al. in a multicentric study did not confirm any change of CCT after treatment with ICAs even after treatment with prostaglandin analogues (19).

In our study on patients who were treated with ICAs there was an increase in CCT values after one year. An increase was recorded in the great majority of patients from this group. Although the results of the difference in CCT are statistically significant after twelve months of observation, it is necessary to note the drop in the number of eyes by 17% (48 eyes), in one part of the patients treatment was combined with beta blockers. In addition, the greatest variability of the inter-year change of CCT in individual patients was demonstrated in this group. Miglior (20) states variability of measurement by ultrasonic pachymetry at more than 15 μm, despite the fact that the examination is conducted by the same doctor.

With regard to the fact that there are several factors which can influence CCT (physiological fluctuation of corneal thickness throughout the day, age, level of oestrogen in women), it is not possible to consider the therapy to be unequivocally the sole basis of the changes in corneal thickness. In studies that confirmed an increase in CCT, this mostly concerned corneas with impaired quality of the endothelium (16). In our study sample the endothelium was not evaluated.

Several works focusing on the change of CCT in patients treated with ICAs have been published in the literature (11, 16-18), though little is known about the influence of ICAs on the biomechanical properties of the cornea (21).

In our group treated with ICAs, the values of CH and CRF are approximately the same after one year as at the baseline measurement. The biomechanical properties of the cornea were unchanged.

Prostaglandin analogues and prostamides, currently the most frequently used group of pharmaceuticals, also have the potential to influence the morphological and biomechanical properties of the cornea. Despite the fact that their mechanism of effect on a cellular level has not yet been fully clarified, theoretically their primary effect is explained by an increase of activity of the enzyme matrix metalloproteinase (MMP) type 1, 2 and 3 (22). MMP is a group of 20 types of enzymes which are present in the anterior segment of the eye: in the lacrimal film, in the conjunctiva, in the epithelium, the stroma and endothelium of the cornea, in the scaffold, in the intraocular fluid and the lens. They share in the degradation of ECM particles and basal membranes (23).

In patients treated with prostaglandin analogues, the increase in the activity of MMP leads to a reduction in immune response and a subsequent decrease in collagen I, III and IV in the extracellular matrix of the smooth muscle tissue of the corpus ciliare and adjacent sclera. As a consequence of this process, uveoscleral outflow increases, leading to a reduction of intraocular pressure (10). Under the influence of prostaglandin analogues, activation of MMP enzyme was also confirmed in the conjunctiva of rabbits (12), with a subepithelial reduction in the thickness of the collagen band of the conjunctiva (12). A less clarified area is the influence of MMP on the physiological function of keratocytes (fibroblasts) in the corneal stroma.

Wu et al. (9) studied changes in artificially cultivated corneal stromal cells following the application of latanoprost. Immunofluorescent staining demonstrated a change in the biosynthesis of cells, which was manifested in a change in the distribution of collagen type I, a decrease in the migration of cells and a decrease in fibronectin.

Liu et al. (24) detected in an experimental model that artificially cultivated corneal fibroblasts contract following exposure to latanoprost, in contrast with timolol, after which they remain unaffected. There is also a reduction in the gel of the collagen fibres for the production of which fibroblasts are responsible. With regard to the fact that ECM represents a significant part of the volume of the corneal stroma and determines its shape and thickness, a theoretical hypothesis has emerged as to whether prostaglandin analogues alter the volume of ECM and CCT.

Viestenz et al. (25), in a randomised controlled trial, published a reduction of CCT in a group treated with prostaglandin analogues, whilst a control group and a group treated with ICAs did not demonstrate these changes. Certain differences reached up to 60 μm over the course of several months of treatment.

Schlote et al. (26) observed the influence of travoprost on CCT. Within an observation period of 12 months there was a reduction in the first 6 months, in the next 6 months the differences were not significant.

Zhong et al. (27) assessed the influence of prostaglandin analogues on CCT over an observation period of 17.19 ± 15.71 months in 69 eyes of newly treated patients with glauco-

ma, and demonstrated a reduction of CCT in the case of latanoprost (14.95 ± 5.04 μm), travoprost (15.73 ± 3.25 μm) and bimatoprost (17.00 ± 6.23 μm). The reduction of CCT did not influence changes in the measured values of IOP.

By contrast, a slight increase of CCT following treatment with prostaglandin analogues was determined by Bafa et al. (28). This concerned 108 eyes of patients with newly diagnosed glaucoma treated by prostaglandin analogues (latanoprost, travoprost and bimatoprost). Within the observation period of two years there was a constant increase in CCT by 1.85-8.83 μm in the period of all follow up visits in the group treated with bimatoprost and latanoprost. In the case of travoprost CCT remained unchanged.

In our study on patients who were treated with prostaglandin analogues, there was a reduction in the values of CCT after one year, the median of the values was -15 μm. A reduction was recorded in all patients from this group, in half of these the reduction was greater than 15 μm.

The conclusions ensuing from the studies on the influence of prostaglandin analogues on CCT on patients with glaucoma are equivocal. However, the majority, in accordance with our results, confirm the opinion that prostaglandin analogues may reduce CCT. If there had been a thinning of the cornea due to the influence of prostaglandin analogues and we had evaluated this influence on the precision of measurement of intraocular pressure by applanation separately, the measured results of IOP would have been undervalued.

However, the precision of measurement of IOP is dependent not only on CCT but also on the curvature of the cornea and its biomechanical properties. The resistance which the cornea manifests to deformation during applanation depends more on viscoelasticity and its rigidity than its thickness. From this perspective we focused more on the issue of the influence of prostaglandin analogues on the biomechanical properties of the cornea before and after the application of treatment.

In the group we treated with prostaglandin analogues, a significant difference in the biomechanical properties of the cornea was determined after one year in comparison with the baseline measurement in the quantities of CH and CRF on a 1% level of significance ($p < 0.001$). There was an increase by approximately 2 units. In one half of the patients from this group, the increase was greater than 2 units.

A number of studies have been published in the literature, which explain changes of CH and CRF following the application of treatment by prostaglandin analogues depending on IOP.

In a study on patients with angular glaucoma (29, 30) in whom high IOP values were measured, low CH values were measured and vice versa. Following a reduction of IOP by surgical treatment, there was an increase in the value of CH. Agarwal (31) confirmed this also by observing CH before and after application of treatment by prostaglandin analogues. He came to the conclusion that knowledge of the baseline value of CH before the commencement of treatment with prostaglandin analogues could indicate the size of the reduction in IOP to be expected. In patients where the baseline value of CH is higher, it is possible to expect a smaller reduction of IOP by prostaglandin analogues.

In the study sample we observed this theory was not confirmed, in patients with a higher CH value there was a sufficient reduction of IOP and vice versa. Similarly, a correlation analysis did not demonstrate a mutual dependency of IOPcc and CH ($R = 0.027$) at baseline and ($R = 0.072$) after one year, and between IOPcc and CRF ($R = 0.204$) at baseline and ($R = 0.139$) after one year.

Another potential factor with an influence on the result of CH and CRF may be an error of measurement of CH in the case of extremely high values of IOP. The maximum power of air flow which the ORA instrument is capable of is not enough to ensure sufficient indentation of the cornea and therefore measures a falsely low CH value (32).

It was also determined by means of a more detailed analysis of the measured curves that the instrument is not capable of identifying certain movement of the eye and this dynamic of the bulb may also cause an error of measurement.

And finally, prostaglandin analogues may genuinely influence the structure of the cornea – the structure of the collagen fibres as is demonstrated by experimental studies (10, 24). The viscoelastic properties of the cornea are altered independently of CCT and IOP. A question remains as to whether the ORA instrument has sufficient sensitivity and specificity to record this change reliably.

## CONCLUSION

Biomechanical properties of the cornea – according to a range of studies, hysteresis (CH) appears to be a parameter which could predict the progression of glaucoma. It is stated that CH indirectly represents the integrity and viscosity of the lamina cribrosa, and a lower CH value is a risk factor for the progression of glaucoma (33). However, to date the use of the CH value, measured by an ORA instrument, as a risk factor in the progression of glaucoma has its limits. The same CH value may express various proportions of elasticity and viscosity (34).

In the assessed group of eyes with newly diagnosed glaucoma and ocular hypertension, we determined different biomechanical properties of the cornea following the application of treatment in patients treated with prostaglandin analogues.

In the quantities of both CH and CRF, a statistically significant difference was demonstrated after one year in comparison with the baseline measurement ($p < 0.001$). The CH and CRF values increased.

Carboanhydrase inhibitors did not alter the biomechanical properties. The control group of healthy eyes and ocular hypertension without treatment also manifested no change.

In the control group of ocular hypertension without treatment, there was a greater representation of eyes with a rigid cornea and cornea of above-average thickness. This confirmed the importance of measuring CH and CRF in addition to CCT in patients with OH in order to ensure that therapy is not commenced prematurely.

Although it is not possible to draw unequivocal conclusions from the results of our study, we wished to draw attention to the possible influence of prostaglandin analogues on the biomechanical properties of the cornea during long-term treatment and thus also to the possible influence of the precision of IOP measurement on the course of treatment. At present it is evident that ORA does not differentiate the proportion of elasticity from the proportion of viscosity in the measured CH value. It shall be necessary to conduct further studies in order to confirm the influence on the long-term administration of prostaglandin analogues on the precision of measurement of intraocular pressure using a new generation of instruments, which analyse elasticity and viscosity separately in more detail.

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# 100th Anniversary of the Birth of Dr. Jozef Slávka

On 27 September 2014 we commemorate the 100th anniversary of Dr. Jozef Slávka, head physician at the department of ophthalmology in Trenčín.
He was born in Nesvady, and attended secondary school in Trenčín. He studied medicine in Bratislava, where he graduated in 1940. Following his graduation he was enlisted in the forces and worked as a military doctor. In 1944 he took part in the Slovak National Uprising. After completing his military service he worked for a brief period in the surgical department in Martin, from where he progressed to the department of ophthalmology, which was then headed by Professor Pajtáš.

In 1949 he became the head physician at the newly founded department of ophthalmology in Trenčín, with a provisional location and equipment. After the completion of the construction of the new pavilion, which was opened in 1954, he enthusiastically set about building a 34-bed department, which he headed until his retirement.
As a skilled ophthalmic surgeon he always devoted a special interest to surgery, in particular on the lacrimal duct and cataract surgery. He was one of the first ophthalmologists in Slovakia to perform a dacryocystorhinostomy. He passed on his wealth of technical and professional experience to his students, who he trained to become well prepared ophthalmologists.
Dr. Slávka's personal interests included the natural sciences and advances in technology. He made use of his knowledge of these areas and his manual dexterity in implementing his proposals for improvement, which were demonstrated to be effective in practice. He also enjoyed photography.
His knowledge of foreign languages also made a contribution to his work. He retired in 1982 and died twenty years later in 2002.

On behalf of his colleagues.

ORIGINAL ARTICLE

# Retinal Tamponade with Silicone Oil – Long Term Results

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## SUMMARY

**Aim:** The aim of this study is to evaluate the frequency and efficacy of silicone oil (SO) retinal tamponade in various retinal diseases. The incidence of silicone oil tamponade according to individual indications, incidence of complications and duration of tamponade were evaluated in the study.
**Material and Methods :** A retrospective study included 510 eyes that were operated on pars plana vitrectomy (PPV) from January 2010 to December 2012. In our group we evaluated 241 men and 189 women, age 4-84 years, mean 62 years . Follow-up period was 12 to 48 months, an average of 27.5 months . We evaluated 253 eyes with diabetic retinopathy, 201 eyes with regmatogenous retinal detachment, 34 eyes with endophthalmitis and 22 eyes after the injury.
**Results:** In 253 diabetic retinopathy eyes (DR) silicone oil tamponade was indicated in 56 eyes (22.1 %). Silicone oil removal was done on 22 eyes (39.3 %), the average length of SO tamponade was 9.7 months. After SO removal BCVA (best corrected visual acuity) 0,1 and worse had 12 eyes (54,6 %), 0,2 – 0,4 had 5 eyes (22,7 %) and 0,5 or better had 5 eyes (22,7 %). Permanent SO tamponade was left in 34 diabetic retinopathy eyes (60.7 %). Secondary glaucoma (SG) was present in 40 eyes (71.5 %). In 201 retinal detachment (RD) eyes silicone oil tamponade was used in 76 eyes (37.8 %). Secondary glaucoma was present in 31 eyes (40.8 %). Silicone oil was successfully removed in 40 eyes (52.6 %), the average length of tamponade was 9.2 months. In this group BCVA 0,1 and worse had 22 eyes (55,0 %), 0,2 – 0,4 had 15 eyes (37,5 %) and 0,5 or better had 3 eyes (7,5 %). 36 eyes (47,4 %) RD eyes had permanent silicone oil tamponade. In a group of 34 eyes with endophthalmitis SO tamponade was used in 16 eyes (47 %). Secondary glaucoma was present in 3 eyes (18.8 %). Silicone oil removal we did in 11 eyes (68.8 %), the average length of SO tamponade was 5.5 months. After SO removal BCVA 0,1 and worse had 3 eyes (27,2 %), 0,2 – 0,4 had 4 eyes (36,4 %) and 0,5 or better had 4 eyes (36,4 %). 5 eyes (31.2 %) with endophthalmitis had permanent SO tamponade. Out of 22 eyes with eye injuries SO tamponade was used in 14 eyes (63.6 %). 5 eyes (35.7 %) had secondary glaucoma. In 9 eyes (64.3 %) silicone oil was removed, the average length of tamponade was 9.1 months. In this group BCVA 0,1 and worse had 6 eyes (66,7 %), 0,2–0,4 had 1 eye (11,1 %) and 0,5 or better had 2 eyes (22,2 %). Permanent silicone oil tamponade had 5 eyes (35,7 %). In group of 56 phakic eyes (100 %) with silicone oil tamponade we followed cataract progression. 26 eyes (40 %) had cataract surgery in 6 month follow up, 47 eyes (72.3 %) in 1 year follow up and 57 eyes (87.7 %) had cataract surgery in 3 years follow up.
**Conclusion:** Silicone oil tamponade is the method of choice for long-term and stable retinal tamponade, which is important for good functional outcomes of the surgical intervention. The silicone oil tamponade of the retina is nowadays irreplaceable, despite of its potential risks and complications.

**Key words: keratoconus, corneal cross-linking, riboflavin, UVA irradiation, maximum curvature of the cornea, effectivity of the treatment**

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## INTRODUCTION

Silicone oil is applied to the vitreous cavity, with the aim of ensuring long--term and stable retinal tamponade (15). In the majority of cases this concerns complicated findings, for which temporary gas tamponade is insufficient. We indicate SO tamponade in the case of retinal detachment for numerous, large or enormous ruptures (14), for proliferative vitreoretinopathy (PVR), severe myopia with macular hole (16) or for repeat operations on retinal detachment (11). In the case of diabetic retinopathy, we most frequently use SO on advanced tractional or combined retinal detachment, or recurrences of haemophthalmos. Further indications are traumas with retinal crack or retinal detachment (3), endophthalmitis (4), CMV retinitis, acute retinal necrosis, complications in age related macular degeneration (ARMD), tumours, retinopathy of prematurity, vein occlusions, Coats' disease and others (2). We consider tamponade with silicone oil during PPV also upon complicated findings in the

sole functioning eye or in the case of severely ill patients and patients with mobility problems.
The silicone oil used in ophthalmology is highly biocompatible. From a chemical perspective it concerns 100% polydimethylsiloxane (purified), its density is 0.97-0.98 g/cm3 (it is therefore lighter than water), refractive index 1.40, surface tension on the interface with water 40 dyn/cm2. Silicone oil is available in various viscosities: 1000, 1300, 2000, 5000, 5500 cs (centistokes). A separate group comprises heavy silicone oils, which we do not use due to their limited indications and complications.
The most frequent complications upon retinal tamponade with silicone oil are cataract and secondary glaucoma. We analyse our results and a comparison thereof with those of other authors in further detail in the discussion. In the case of secondary glaucoma, we achieved sufficient compensation of IOP (intraocular pressure) in the majority of eyes by means of local therapy, upon surgical treatment in our workplace we give priority to cyclodestructive surgery due to the risks and complications of filtering operations on the eye with simultaneous tamponade with silicone oil.
As a consequence of its higher refractive index in comparison with water or the vitreous body, silicone oil causes a refractive shift. Upon aphakia it causes a reduction of hypermetropia, in phakic or pseudophakic eyes it causes a shift to hypermetropia. In the case of severe myopia it reduces myopic correction.
A highly unpleasant complication of SO tamponade is its subretinal or subchoroidal penetration, mostly as a consequence of PVR, scarring of the retina or choroidea upon findings of complicated retinal detachment or in the case of traumas. In the case of penetration of SO beneath the conjunctiva, which is very difficult to remove, infiltration of the Tenon's capsule occurs, resulting in chronic inflammation. For this reason, in the case of sutureless PPV techniques we consider it safer to suture all wounds upon the use of SO tamponade, thus averting this complication. In rare cases, penetration of SO may occur into the conjunctiva via a glaucoma drained implant (10).
A less frequent complication of long-term SO tamponade is zonular keratopathy, which probably occurs as a consequence of impaired trophic function of the anterior segment in severely afflicted eyes which would otherwise probably atrophy without SO (1).
The causes of deterioration of central visual acuity following evacuation of SO are sometimes not entirely clear. Phototoxicity of the light used in PPV, toxicity of SO with regard to the retina and also the effect of the enlarged image during SO tamponade, which is lost after evacuation, may play a role in this process (7).

## MATERIAL AND METHOD

A retrospective study incorporated 510 eyes of 430 patients, who were operated on using the technique of pars plana vitrectomy (PPV) from January 2010 to December 2012 (36 months). The study sample comprised 241 men and 189 women, aged 4 – 84 years, average 62 years. The observation period was 12 – 48 months, average 27.5 months. We evaluated 4 sub-groups within the study: 253 eyes with diabetic retinopathy, 201 eyes with rhegmatogenous retinal detachment, 34 eyes with endophthalmitis and 22 eyes following trauma. With regard to the small number of patients, we did not evaluate SO tamponade statistically in other indications. In addition to the above-stated disorders, 6 eyes were indicated for SO tamponade during the observation period with uveitis, 2 eyes with wet form ARMD, 1 eye with intraocular tumour, 1 eye with retinopathy of prematurity, 1 eye with Coats' disease and 1 eye with central retinal vein occlusion.
In the study we evaluated the indications, frequency, anatomical and functional results of retinal tamponade with silicone oil (SO) in the case of various ocular pathologies, as well as the incidence of secondary glaucoma and its solution.
BCVA was evaluated on Snellen's optotypes in all eyes at the end of the observation period.
In the study we also evaluated the incidence and progression of cataracts as a consequence of tamponade with silicone oil and the necessity of surgical solution thereof.

## RESULTS

In the sub-group of 253 eyes (100%) with diabetic retinopathy (DR), tamponade with silicone oil was indicated in 56 eyes (22.1%). Silicone oil was evacuated in 22 eyes (39.3%), the average length of tamponade was 9.7 months. In the sub-group of eyes with diabetic retinopathy, permanent SO tamponade was left in 34 eyes (60.7%). Out of 22 eyes following successful evacuation of SO we attained BCVA of 0.1 and worse in 12 eyes (54.6%), 0.2 – 0.4 in 5 eyes (22.7%) and 0.5 and better in 5 eyes (22.7%). Out of 34 eyes with retained permanent SO tamponade we attained BCVA of 0.1 and worse in 33 eyes (97.1%), and 0.2 – 0.4 in only 1 eye (2.9%). We recorded secondary glaucoma as a consequence of SO tamponade in 30 eyes (53.6%), and recorded decompensation of pre-existing secondary neovascular glaucoma in 10 eyes (17.9%). Secondary glaucoma was present in the sub-group of eyes with DR and with applied SO in as many as 40 eyes (71.5%)! Of these, 37 eyes (92.5%) were compensated in local therapy, in 3 eyes (7.5%) a cyclocryo application operation was performed with a good effect.
In the sub-group of 201 eyes (100%) with rhegmatogenous retinal detachment (RRD), primary SO tamponade was indicated in 51 eyes (25.4%), and secondary SO tamponade was indicated in 25 eyes (12.4%) following previous unsuccessful PPV with expansive gas tamponade. Altogether SO tamponade was used on 76 eyes (37.8%) with RRD. Silicone oil was successfully evacuated in 40 eyes (52.6%). The average length of tamponade was 9.2 months. In 7 eyes (15% of eyes following evacuation of

Table 1

| Indication | SO | Secondary | Glaucoma | Permanent tamponade | Successful evacuation of SO |
|---|---|---|---|---|---|
| DR | n = 253 | 56 (22.1%) | 40 (71.5%) | 34 (60.7%) | 22 (39.3%) |
| Rhegmatogenous RD | n = 201 | 76 (37.8%) | 31 (40.8%) | 36 (47.4%) | 40 (52.6%) |
| Endophthalmitis | n = 34 | 16 (47%) | 3 (18.8%) | 5 (31.2%) | 11 (68.8%) |
| Traumas | n = 22 | 14 (63.6%) | 5 (35.7%) | 5 (35.7%) | 9 (64.3%) |

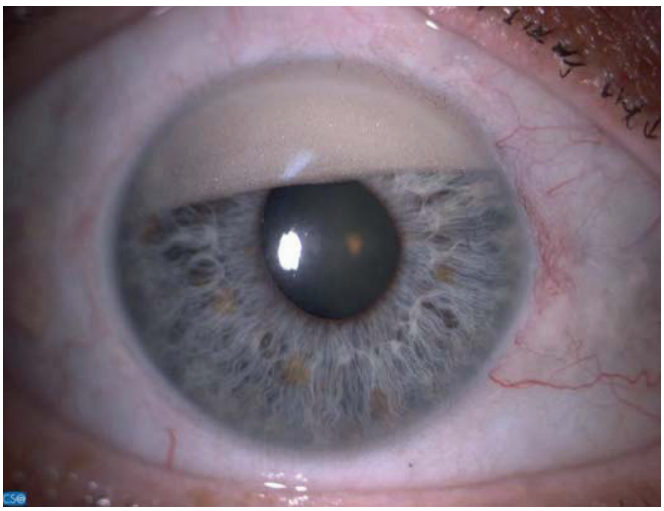

**Fig. 1** Emulsification of SO in anterior chamber

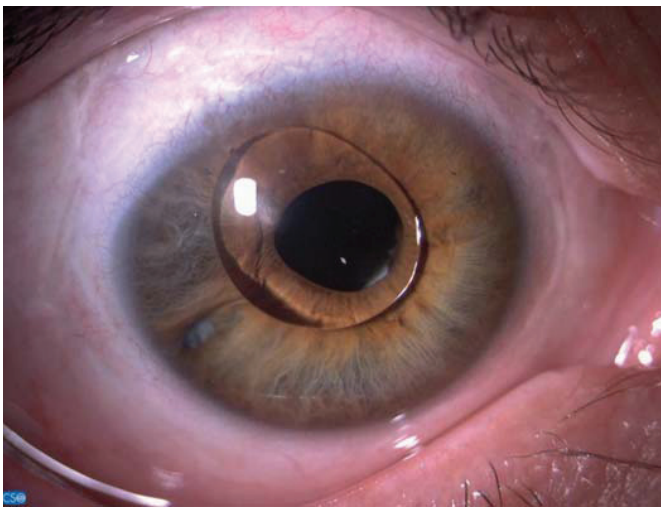

**Fig. 2** Silicone oil in anterior chamber

SO), silicone oil was re-applied due to the recurrence of retinal detachment in our sub-group. Permanent retinal tamponade using SO was retained in 36 eyes (47.4%). Out of 40 eyes following successful evacuation of SO we attained BCVA of 0.1 and worse in 22 eyes (55.0%), 0.2 – 0.4 in 15 eyes (37.5%) and 0.5 and better in 3 eyes (7.5%). Out of 36 eyes with retained permanent SO tamponade we attained BCVA of 0.1 and worse in 32 eyes (88.9%), and 0.2 – 0.4 in only 4 eyes (11.1%). We recorded secondary glaucoma in 31 eyes (40.8%) with SO tamponade for RRD. In 29 eyes (93.5%), IOP was compensated local therapy, in 2 eyes (6.5%) we proceeded during SO tamponade to transscleral cyclophotocoagulation by diode laser, with a good effect.

In the sub-group of 34 eyes (100%) with endophthalmitis, SO tamponade during PPV was indicated in 16 eyes (47%). Silicone oil was evacuated in 11 eyes (68.8%), the average length of tamponade was 5.5 months. Permanent SO tamponade was left in 5 eyes (31.2%) with endophthalmitis. Out of 11 eyes following successful evacuation of SO we attained BCVA of 0.1 and worse in 3 eyes (27.2%), 0.2 – 0.4 in 4 eyes (36.4%) and 0.5 and better in 4 eyes (36.4%). Out of 5 eyes with retained permanent SO tamponade we attained BCVA of 0.1 and worse in 5 eyes (100%). We recorded secondary glaucoma as a consequence of SO tamponade in 3 eyes (18.8%), in all IOP was compensated in local therapy.

In the sub-group of 22 eyes (100%) with ocular trauma, SO tamponade was indicated in 14 eyes (63.6%). We performed evacuation of silicone oil in 9 eyes (64.3%), the average length of tamponade was 9.1 months. Permanent SO tamponade was left in 5 eyes (35.7%). Out of 9 eyes following evacuation of SO we attained BCVA of 0.1 and worse in 6 eyes (66.7%), 0.2 – 0.4 in 1 eye (11.1%) and 0.5 and better in 2 eyes (22.2%). Out of 5 eyes with retained permanent SO tamponade we attained BCVA of 0.1 and worse in 5 eyes (100%). We recorded secondary glaucoma in 5 eyes (35.7%), in all eyes IOP was compensated in local therapy.

An overview and comparison of the evaluated results is presented in table 1.

In the total group of 162 eyes (100%) with SO tamponade, 15 eyes (9.3%) were aphakic, 66 eyes (40.7%) pseudophakic and 81 eyes (50%) phakic. During the primary operation we conducted combined cataract surgery with PPV on 16 eyes (19.8%). In the observation period we evaluated the incidence of cataract with the need for surgery by the technique of phacoemulsification with or without the implantation of an artificial IOL (intraocular lens) in the group of 65 phakic eyes (100%). Within six months 26 eyes were operated on (40%), within 1 year 47 eyes (72.3%) were operated on, within 3 years 57 eyes (87.7%). Of these, 32 eyes (49.2%) were operated on for cataract during tamponade with silicone oil, in 5 eyes (7.7%) surgery was performed without the implantation of an IOL.

## DISCUSSION

The most frequent complication of retinal tamponade with silicone oil is cataract, the incidence of which changes depending on the age of the patient, associated general illnesses and ocular pathologies, and naturally also the length of SO tamponade. In our study sample we observed a progression of cataract within 1 year in 72.3% of eyes, within 3 years in as many as 87.7% of eyes. This data is even higher than the published results of other authors (5), who describe the presence of a cataract in 50% within 5 years following PPV, in diabetics in up to 80%. From this it is evident that the presence of silicone oil tamponade has a significant influence on the metabolism of the lens. In the era of modern phacoemulsification, cataracts do not represent a more serious technical problem. However, in the postoperative period a progression of secondary fibrosis occurs, with a thickening of the posterior capsule of the lens. As a result, upon the subsequent evacuation of SO it is usually necessary to perform posterior capsulectomy. For the above reasons, the optimal solution is combined surgery of the anterior and posterior segment of the eye with implantation of a posterior chamber lens into the capsule and subsequent PPV. However, we attempt to avoid this in patients with preserved accommodation.

From our perspective, the most serious complication of retinal tamponade with silicone oil is secondary glaucoma (17), which frequently requires combined local therapy, sometimes we also embark upon surgical correction of raised intraocular pressure. This is most frequently caused by emulsifications of SO (fig. 1), which clog the trabecular meshwork and thereby cause outflow of the fluid

from the anterior chamber. From the perspective of long-term tamponade it appears to be more appropriate to use silicone oil with a higher viscosity (5000-5500cs) (18). In our groups, its incidence was 18.8-71.5%, which corresponds to the data from the literature (8). Most frequently (71.5%) this was in eyes with diabetic retinopathy, where secondary neovascular glaucoma plays an important role (19).

Closed-angle secondary glaucoma may occur as a consequence of pupillary block, which is preceded by basal iridectomy at 6 o' clock ("Japanese"). Silicone oil in the anterior chamber (fig. 2) can cause blockage of the outflow of the intraocular fluid in the chamber angle, as a result it is necessary to evacuate the silicone oil from the anterior chamber perioperatively or postoperatively using fluid or viscoelastic material (12).

In the sub-group of eyes with rhegmatogenous retinal detachment, silicone oil was successfully evacuated in 40 eyes (52.6%). In the Silicone Oil Study, SO was successfully evacuated in 45% of cases (9). In our study sample, silicone oil was re-applied in 7 eyes (15% of eyes following evacuation of SO) due to recurrence of retinal detachment. This data corresponds with the data of other authors in the literature, who have referred to the necessity of reoperation of retinal detachment following evacuation of SO in 15-25% of eyes (6, 13). It is evident that the percentage success rate of evacuation of SO upon RRD remains comparable, but it is necessary to note that we choose SO tamponade today in the case of more complicated findings of retinal detachment, whilst we resolve simpler findings with the aid of expansive gas tamponade.

In the sub-group with endophthalmitis we successfully evacuated SO in 11 eyes (68.8%). In a similar group of patients, the authors Dotřelová et al. (4) explanted silicone oil after 4.6 months in 40.9% eyes. We believe that we achieved better results thanks to timely surgical intervention, which thereby improves the prognosis with regard to anatomical and function aspects.

We achieved similar results in comparison with other authors (3) also in the case of ocular traumas (3). Doležalová et al. in their study referred to successful evacuation of SO in two eyes out of four (50%) following PPV for severe perforating ocular trauma.

## CONCLUSION

Retinal tamponade with silicone oil is irreplaceable, despite the potential risks and complications in vitreoretinal surgery. The anatomic success rate following evacuation of the silicone oil provides the preconditions for a successful functional result. Thanks to advances in the technical possibilities of PPV and timely surgical intervention, the proportion of successful evacuations of SO is increasing (68.8% in the sub-group of eyes with endophthalmitis). In primary pars plana vitrectomy we always attempt to avoid retinal tamponade with silicone oil, which is possible thanks to retinal tamponade with expansive gases. Primary SO tamponade is thus indicated later for more complicated findings in the posterior segment of the eye. Thanks to expansion gases, the absolute number of patients with permanent retinal tamponade with SO has been reduced. The decision on the type of tamponade always depends on the individual case, the finding on the ocular fundus and also on the anterior segment of the eye, as well as on the preferences and experiences of the vitreoretinal surgeon. In our workplace SO tamponade is indicated most frequently in the case of PPV for trauma – in 63.6% of eyes. We recorded secondary glaucoma upon SO tamponade following PPV for diabetic retinopathy – in 71.5% of eyes. On average, we embark upon evacuation of SO after 5.5 to 9.7 months. The anatomical success rate of evacuation was 39.3% - 68.8%, which corresponds with the published results of other authors (9). Permanent retinal tamponade using SO was retained in our patients in 31.2% - 60.7% of cases, most frequently following PPV for diabetic retinopathy.

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ORIGINAL ARTICLE

# The Incidence of Endophthalmitis after the Application of Intravitreal Injections in FNKV with Regard to Various Prophylactic Antibiotic Regimens

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## SUMMARY

**Aim:** Comparing the incidence of endophtalmitis at the Ophthalmologic clinic of FNKV after the application of intravitreal injections with regard to various prophylactic antibiotic regimens.
**Methodics:** Comparing the number of endophtalmitis cases during the period of 2005–2011, when the intravitreal applications were secured by full antibiotic prophylaxis (Floxal)/Oftaquix gtt. 5xd 3 days before the application and 3 days after the application with the years of 2012–2013, when Vigamox gtt. was used during the preparation of the eye before surgery to prevent inflammatory changes.
**Results:** In the years of 2005–2013, 5005 injections were applied. In total we recorded three cases of endophthalmitis. In all cases, a pars plana vitrectomy with sample collection for culture and microbiological analysis was performed. During the years of 2005–2011, 2 651 injections were applied with two cases of endophtalmitis (0,075%, 1:1 325, both cases culture-negative). During the years of 2012–2013, 2 355 injections were applied with one case of endophtalmitis (0,042 %, 1:2 355, culture-positive).
**Conclusion:** According to our experience, limited prophylactic antibiotic regimen does not increase the incidence of endophtalmitis in comparison with full prophylactic antibiotic regimen.

**Key words: intravitreal injections, antibiotic, endophtalmitis, prophylactic**

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## INTRODUCTION

In the last few years there has been a marked increase in intravitreal applications, primarily in connection with the use of anti-VEGF (vascular endothelial growth factor) preparations. The main indication for their use is wet form age-related macular degeneration (ARMD), and more recently macular edema complicating retinal vein occlusion and diabetic macular edema. A smaller group is represented by other diagnoses, such as neovascular glaucomas, macular edemas of other etiology, neovascular choroidal membrane of origin other than ARMD etc. Other substances applied to the vitreous cavity in the Czech Republic also include corticosteroids (in the form of triamcinolone acetonide (TMC) solution and in depot form – dexamethasone (Ozurdex)), in particular for the treatment of macular edemas.
Because the number of these procedures is constantly increasing, it is necessary to reckon with certain relatively rare, but nevertheless very serious complications for the prognosis of the eye. One of the most serious and most feared complications is indisputably endophthalmitis (29). A logical measure to reduce the incidence of endotphalmitis was the use of topical antibiotic (ATB) prophylaxis before and after the application of the intravitreal preparation. The original standard schema was the use of ATB drops five times per day, three days before and three days after the application. Despite the fact that this prophylaxis reduces bacterial growth (25), to date no unequivocal data has been published in support of the use of this preventive treatment with regard to reducing the incidence of endophthalmitis (3, 5, 32, 35). In what is probably the largest published study to date, the authors Storey et al. (33) analysed a total of 117 171 applications with a total number of 44 suspected cases of endophthalmitis (0.038%), 1 case per 2663 injections), of which 17 were culture-positive (0.0170, 1 per 5 765 injections). Upon the use of ATB (57 654 applications), there was an incidence of 28 cases of suspected endophthalmitis (0.049%, 1 per 2 059 applications). Without the use of ATB (34 900 applications) there was an incidence of 11 cases (0.032%, 1 per 3 173 applications).
Our study analyses the effect of full and partial ATB prophylaxis following the application of an intravitreal preparation at the Ophthalmology Clinic at the Královské Vinohrady University Hospital (FNKV).

## METHOD

This represents a retrospective evaluation of serious inflammatory complications following intravitreal applications at the Ophthalmology Clinic of FNKV. The analysed study sample included all patients who had undergone an application of intravitreal preparations 30Ga by injection – Lucentis, Avastin, TriamHEXAL, Macugen – in the period 2005-2013.
The incidence of endophthalmitis was compared in two groups of patients. In

the first group of patients, the topical ATB Ofloxacin (Floxal) or Levoflaxin (Oftaquix) was used in a standard regimen according to the Summary of Product Characteristics (SPC) for Lucentis five times per day 3 days before and 3 days after the application. In the second evaluated group, Moxifloxacin (Vigamox) was applied three times during the preoperative preparation – first 30 minutes before the application, second 20 minutes before the application and finally immediately before the application. Moxifloxacin was chosen for its good penetration into the chamber fluid and exceptionally high concentration in the chamber fluid 20 minutes after the first dosage – the concentration is higher than the minimum inhibition concentration of the most common pathogens causing endophthalmitis (21, 16, 13, 18). Another reason for the use of moxifloxacin is the potential effect together with povidone iodine and the low resistance of microbial flora (34).

## APPLICATION TECHNIQUE

Within the years 2005-2012, all the applications were performed in an operating theatre, since 2013 the procedures have been performed primarily in the application ward at the outpatient section of the clinic. In the first observed period, a total of ten doctors applied the injections, in the second period this was performed by a total of five doctors. Before the procedure each patient was examined and then sent to the nurse for preoperative preparation. Topical anaesthesia was induced using Benoxi drops. After laying on the operating bed, the eye and its surrounding area was thoroughly disinfected with 5 % povidone iodine (Betadine 5%), which was left to act for at least 90 seconds. A sterile facecloth and mouth gag were used individually according to the customs of the attending doctor, all attending doctors used sterile gloves, a mouthpiece and cap. In a limited prophylactic regimen, the last drop of povidone iodine was applied to this area before the actual application by the nurse. After indication of the place of injection at a distance of 3.5 mm or 4.0 mm from the limbus in the lower temporal quadrant, the doctor applied the pharmaceutical by the standard method using a 30Ga needle (fig. 1). All applications were performed without the use of a surgical microscope. After the application, perfusion of the optic nerve was checked microscopically.

We considered endophthalmitis to cover all conditions with a severe intraocular inflammation process which required a surgical solution (i.e. performance of pars plana vitrectomy or application of ATB preparations into the vitreous cavity). The diagnosis was always determined by an experienced vitreoretinal doctor. We classify above all deterioration of visual acuity, pain and vitritis within the image of endophthalmitis following the application of an intravitreal preparation. Also specific for endophthalmitis is the high speed of these changes. Inflammatory manifestations in the anterior chamber are usually present later, and hypopyon need not be present, such as in certain cases of endophthalmitis, for example following cataract surgery.

A condition for the inclusion of a patient into the study sample was intravitreal application within a short time period before the manifestation of the pathology. These patients underwent pars plana vitrectomy as a therapeutic procedure, with the taking of a sample of the vitreous body for microbiological and histological analysis, and ATBs were subsequently applied to the vitreous cavity.

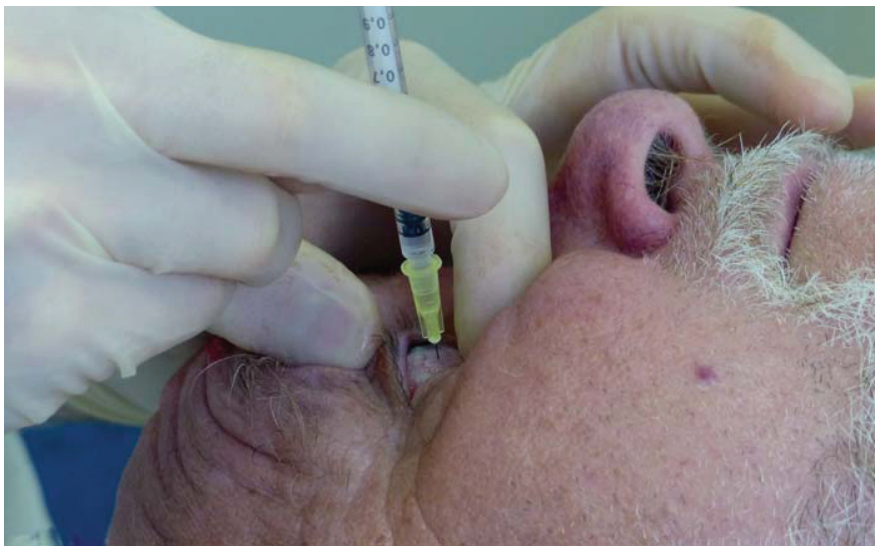


Fig. 1 Technique of intravitreal application

## RESULTS

In the first period (2005-2011) – in ATB prophylaxis according to SPC we applied a total of 2651 injuections (1087 x Macugen, 1092 x Lucentis, 101 x TMC, 371 x Avastin (table 1). Within this period, two cases of endophthalmitis were recorded (both following application of the Lucentis preparation). In both cases, the doctor applied the preparation in the operating theatre, in both cases pars plana vitrectomy was performed with a culture-negative microbiological result. The incidence of endophthalmitis with full prophylactic regimen was 2:2 615 in our clinic, i.e. 0.075%.

In the second observed period (2012-2013), in conditions of reduced ATB prophylaxis, we applied a total of 2 355 injections (155 x Macugen, 1650 x Lucentis, 134 x TMC, 415 x Avastin, 1x Eylea), (table 1, graph 1). In 2012 the applications took place in the operating theatre (1 053 injections), in 2013 the intravitreal injections were administered in the application ward at the outpatient section of the clinic (1 302 injections). During this period one case of endophthalmitis was recorded (following injection with the Macugen preparation). The application was performed in the operating theatre. In this case also, pars plana vitrectomy was performed, this time with a cuture-positive finding (Staphylococcus coagulase-negative). The incidence of endophthalmitis with a limited ATB regimen during this period was 2: 23 55, i.e. 0.042%.

## DISCUSSION

Today endophthalmitis is indisputably one of the most feared complications following the application of intravitreal preparations, and its course is of absolutely fundamental significance for the future of the eye.

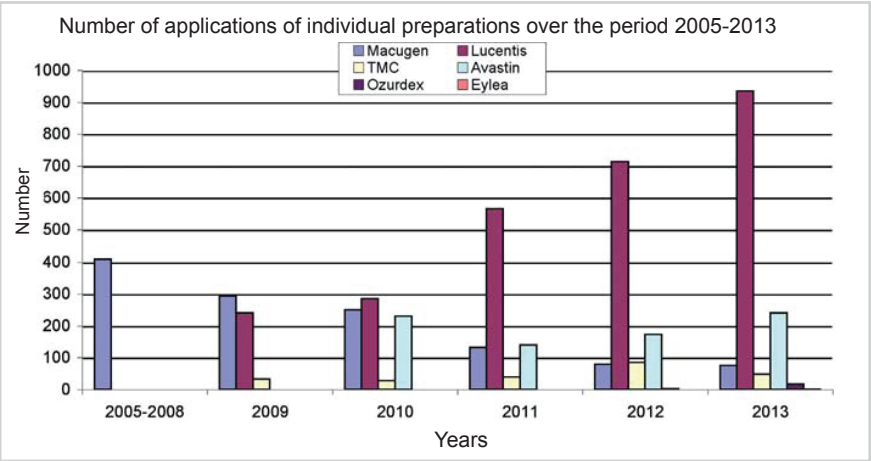
The risk of endophthalmitis following the application of intravitreal preparations differs proportionally in various published studies, from 0.018% to 1.4% (6, 12, 26, 30, 24, 20, 17, 11, 9,

**Table 1** number of applications of individual preparations in years 2005-2012

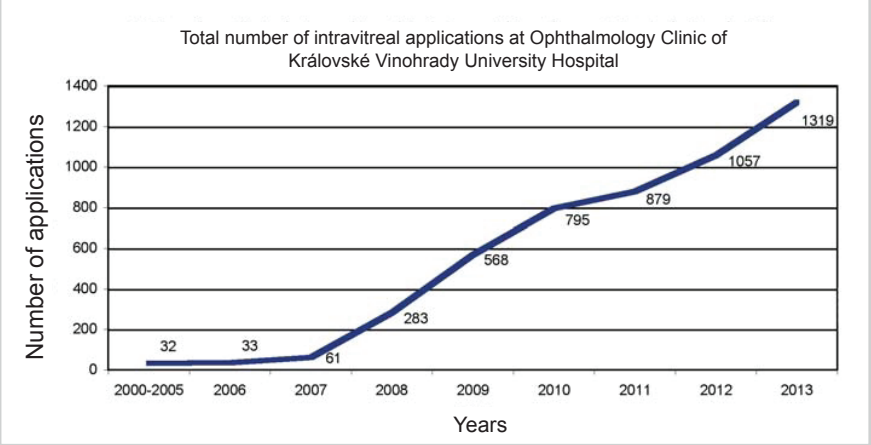
| | 2005-2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|---|
| Macugen | 409 | 294 | 251 | 133 | 79 | 76 |
| Lucentis | 0 | 241 | 285 | 566 | 714 | 936 |
| TMC | 0 | 33 | 28 | 40 | 86 | 48 |
| Avastin | 0 | 0 | 231 | 140 | 174 | 241 |
| Ozurdex | 0 | 0 | 0 | 0 | 4 | 17 |
| Eylea | 0 | 0 | 0 | 0 | 0 | 1 |
| | 409 | 568 | 795 | 879 | 1057 | 1319 |

8, 15, 4, 2, 1, 28). For example, in the large prospective studies "The Minimally Classic/Occult Trial of the Anti-VEGF Antibody RAnibizumab in the Treatment of Neovascular AMD (MARINA)" (27) and "Anti-VEGF Antibody for the Treatment of Predominantly Classical Choroidal Neovascularization in AMD (ANCHOR)" (7), the risk of endophthalmitis was 0.05%. The actual definition of endophthalmitis by the individual authors is of great significance for the determination of the frequency of endophthalmitis in the individual studies. In the above-stated studies MARINA and ANCHOR, there were in total a further 24 patients with manifestations of medium-severe intraocular inflammation who were not included in this study sample, but according to the conventions of the workplace the majority of them received ATBs applied into the vitreous cavity upon demonstration of vitritis. If we included these patients into the group of patients with endophthalmitis, the frequency of endophthalmitis in the MARINA study would be 0.22%, and in the ANCHOR study 0.18%, which is an almost four times greater risk than was published.

In recent years, in connection with the wide use of ATBs, there has been frequent talk of an exponential increase in microbiological resistance in all branches of medicine, often with fatal consequences, in particular for otherwise generally weakened patients. The largest share of the blame for creating this situation indisputably lies with the unnecessary overuse of ATBs, and ophthalmology undoubtedly contributes to this situation. In the above-stated two-year studies ANCHOR and MARINA, where the patients applied ATB drops each month before the check-up, there was a high degree of overuse of ATB in our opinion. If we adhered to this schema also in regular practice, especially in the pro re nata (P.R.N.) regimen, each patient would apply ATB drops for at least 36 days per year (3 days x 12 months). This overuse of ATB drops then leads demonstrably to an increase in the resistance of the microbiological flora of the conjunctiva (23), with all the potentially negative consequences.




Graph 1




Graph 2

At a time when the numbers of patients treated for retinal pathologies are constantly increasing (graph 2), with an attendant increase in the numbers of applications of substances to the vitreous body, it is advisable to study the effectiveness of preventive measures against endophthalmitis as the most serious potential complication of this therapy. At various workplaces worldwide today, we encounter diametrically opposite approaches to the application procedure. On the one hand there are workplaces where injections are performed in an operating theatre, the patient is dressed in operating clothing with a cap, the application area is screened off and sterile, a sterile foil is affixed to the eye, the operating surgeon wears a cap, facecloth and uses a sterile empir, sterile gloves are an absolute standard and the application is performed with the use of povidone iodine and several days of prophylactic antibiotic preparation. On the other hand there are workplaces (especially abroad) where the application takes place immediately after indication on an application chair at an outpatient department, frequently without sterile gloves or other special preparation, and the injection may be administered by a nurse (22). Both of these situations have their advantages, either from the perspective of safety in the first case or from the perspective of timeliness of commencement of therapy in the second case; they also have their

disadvantages primarily in the financial, logistical and material securing in the first case, or in the risk of infection complications in the second.

Today several ophthalmologists consider the use of povidone iodine to sterilise the surrounding area of the eye and its surface to be the sole fundamental measure for the prevention of endophthalmitis (31, 26). According to the authors Friedman et al. (10), the time necessary for a significant and sufficient reduction of bacterial flora is 30 seconds. A further observation was that the application of a mouth gag has no influence on the quantity of bacterial flora in the conjunctival sac upon the use of povidone iodine. The study by the authors Chen E LM et al. (14) demonstrated that the majority of microorganisms causing endophthalmitis are commensals of the oral mucous membrane, and as a result both the staff and the patient should avoid speaking or coughing during the application, and that a mouthpiece should be used throughout the entire duration of the application as a prevention against the risk of contamination.

The collective of authors Lam, Waheeb (19) also compared various prophylactic antibiotic regimens. The result was the most favourable in the group of patients who did not use ATBs whatsoever. Upon the use of ATB prophylaxis on the day of application, the incidence of endophthalmitis was the highest – 0.083%, in comparison with 0.061% upon five-day prophylaxis and 0.037% without ATB prophylaxis.

## CONCLUSION

If we take into account the fact that there are various studies (3, 5, 32, 35, 19) that refute the significance of ATB prophylaxis before the application of an intravitreal preparation, it is necessary to ask whether or not this prophylaxis is in fact rather harmful to patients.

Although it is stated that it is possible to reach a statistically significant comparison of various regimens upon a comparison of the incidence of endophthalmitis only upon more than 100 000 applications, according to our experiences it is possible to judge that a heightened prophylactic ATB regimen does not reduce the incidence of endophthalmitis following the application of intravitreal preparations, which corresponds with the results of large foreign studies.

With regard to the above-stated studies and our own experiences, all ATB therapy before and after the application of an intravitreal preparation by a 30Ga needle was discontinued at our workplace as of 1 January 2014, and since that time we have continued to ensure only thorough and careful disinfection of the operating field, adherence to regimen measures and handling of the needle.

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ORIGINAL ARTICLE

# Ocular Disturbances as the First Sign of Decompensated Arterial Hypertension

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## SUMMARY

Arterial hypertension is a serious health problem. Decompensation of blood pressure may cause many ocular complications. We present three case reports of men with decompensated blood pressure and associated ocular complications. Successful compensation of blood pressure leads to objective improvement of fundus changes and vision.

**Key words: arterial hypertension, hypertonic angiopathy, retinopathy, neuropathy**

**Čes. a slov. Oftal., 70, 2014, No. 5, p. 190–194**

## INTRODUCTION

We indicate repeated increase of blood pressure (BP) > 140/90 mmHg measured minimally at two different visits (21) as arterial hypertension. In its high prevalence within the adult population, arterial hypertension represents a serious health problem. In Western industrial countries approximately every second adult lives with blood pressure higher than 140/90 mmHg (12), and overall hypertension afflicts approximately one billion people worldwide (4, 20, 22). The Czech Republic ranks amongst those countries with a high incidence of this disorder. In a randomly selected population sample within the age range of 25-64 years, a 40% prevalence of hypertension was determined, at the age above 65 years hypertension afflicts minimally 60% of the population (5).
Hypertension may manifest itself asymptomatically for several years before it damages the functions of organs, and its clinical course is mostly without symptoms. Only upon a massive increase in pressure do non-specific complaints such as headache, dizziness and epistaxis occur. If hypertension is not diagnosed in a timely manner, it is often not manifested until the occurrence of complications, for example changes on the ocular fundus.
Hypertonic retinopathy is a condition characterised by a spectrum of retinal changes in patients with high systemic arterial blood pressure (16). It was first described by Liebricht in 1859 (11). Data from various international studies shows that signs of hypertonic retinopathy are present in 3-14% of adult individuals aged > 40 years (7, 8, 9, 15, 16, 18, 19, 20). A higher incidence has been determined in men (13). Timely identification of hypertonic retinopathy is an important step in stratification of the risk in patients with hypertension (2, 3).
The usual characteristics of chronic hypertonic retinopathy are: constriction of the arterioles, cotton wool spots, flame-shaped surface haemorrhages, hard exudates and macular edema. In the case of malignant hypertension we also observe signs of neuropathy and choroidopathy on the ocular fundus. The majority of these changes abate over time in the case of compensation of blood pressure (10).

## CASE REPORT 1

The patient, a 39 year old man, was examined at the Department of Ophthalmology at the University Hospital in Hradec Králové due to deterioration of vision in the right eye. From the anamnesis it ensues that the patient had hitherto been treated for dyslipidemia and had regularly used Simvacard 40 mg in a dose of 1 tablet per day. He had experienced headaches for approximately six months without other accompanying complaints. His body mass index was 35.3. His previous ocular anamnesis was without any remarkable features. He had noticed ocular complaints for 14 days and perceived a progressively increasing black stain in the centre of the visual field of the right eye. Initial best corrected visual acuity (BCVA) in the right eye was 20/50. Visual acuity of the left eye was 20/32, and was not improved by correction. Upon measurement of blood pressure, values of 190/130 mmHg were determined.
The finding in the anterior segment of the eye was bilaterally commensurate to age. Cotton wool spots dominated on the ocular fundus, with blurred edges of the discs of the optic nerve and diffuse intraretinal haemorrhages. Constriction of the retinal arterioles and their increased tortuosity, positive phenomena of crossing was determined in the capillaries. In the central region there was bilateral indication of a star-shaped figure, hard exudates, in the right eye with swelling of the macula (fig. 1, 2). Optical coherence tomography (OCT) (HD OCT Cirrus, Zeiss) of the central region of the right eye demonstrated a finding of loose liquid between the neuroretina and

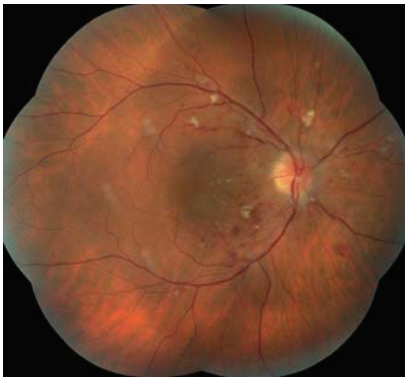

**Fig. 1** Right eye. Disc of the optic nerve with blurred edges. Cotton wool spots and diffuse intraretinal haemorrhages. In the central region there is an indication of a star-shaped figure, macular edema.

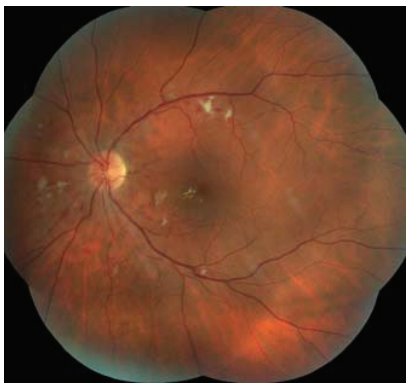

Fig. 2 Similar finding on ocular fundus of left eye

the retinal pigment epithelium (RPE), neuroretinal edema, which continued to the papilla (fig. 3). Central retinal thickness (CRT) was 569 µm. In the left eye the finding on OCT of the macular was commensurate to age. The patient was sent to the Internal Clinic at the University Hospital Hradec Králové for configuration of antihypertensive therapy. Further observation of the development of the disorder was not possible, because the patient did not attend the planned follow-up.

## CASE REPORT 2

The patient, a 59 year old man, was admitted for further examination of an ocular finding at the Department of Ophthalmology at the University Hospital Hradec Králové, due to deterioration of vision in both eyes. He had hitherto been treated generally for psoriasis, which had been stable for the last 20 years, and stated paints in the shoulder joints and cervical spine. For approximately two months he had observed a deterioration of vision in both eyes. Initial BCVA in the right eye was 20/80, in the left 20/100. On the day of admittance, upon measurement of BP values of 210/120 mmHg were determined. On the anterior segment of the eye the bilateral finding was commensurate to age. Upon an examination of the ocular fundus we determined blurred edges and congested discs of the optic nerve, linking to several cotton wool spots. In both eyes there was evident swelling of the macula, in the periphery of the retina we observed diffuse intraretinal haemorrhages, constriction of the

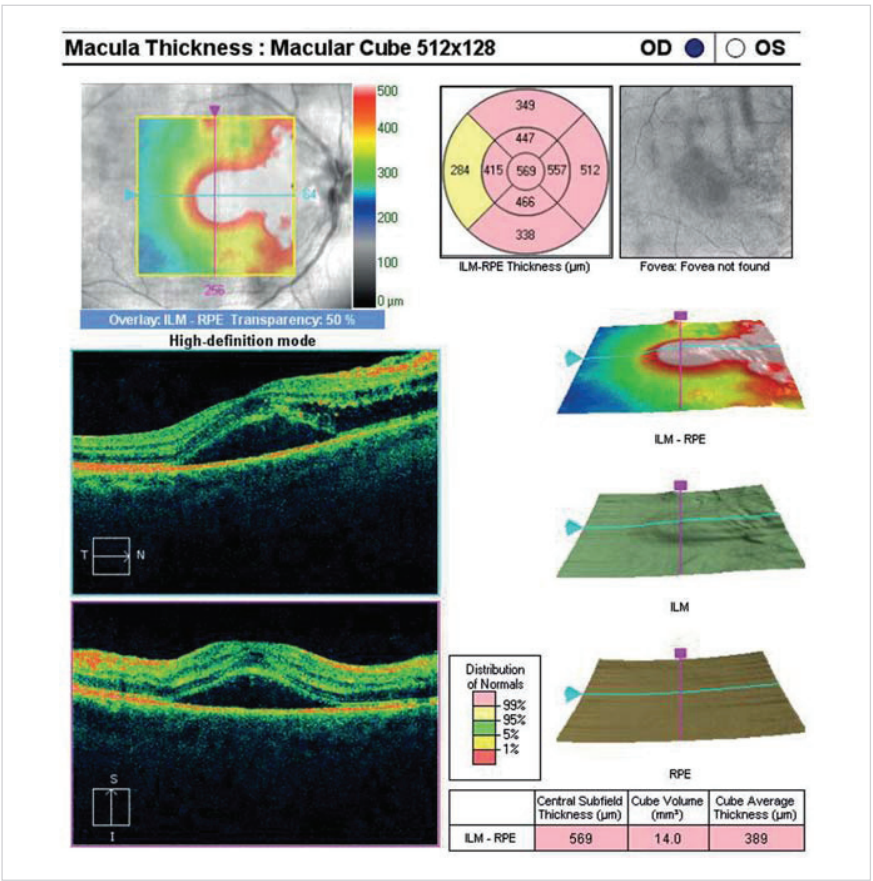


**Fig. 3** OCT of central region of right eye. Finding of loose liquid between neuroretina and retinal pigment epithelium (RPE), neuroretinal edema, which continues in the direction towards the disc of the optic nerve.

**Fig. 4** Right eye. Pronounced hypertonic retinopathy, stage 3-4 according to Keith.

retinal arteriorles and their increased tortuosity, with positive phenomena of crossing (fig. 4). Optical coherence tomography of the central region bilaterally showed cystic neuroretinal edema (fig. 5). Central retinal thickness (CRT) of the right eye was 463 µm, in the left eye 600 µm. We concluded a condition of hypertonic neuroretinopathy with macular edema bilaterally. The patient was transferred according to his place of residence to the Cardiology Department at the Pardubice Regional Hospital for the configuration of antihypertensive therapy. At a follow-up examination one month after the commencement of general therapy: Agen 5 mg (amilpdipine) 0-0-1, Loradur (amiloride 5 mg and hydrochlorothiazide 50 mg) ½-0-0, Betaloc SR 200 mg (metaprolol) ½-0-0, blood pressure was compensated to values of 130/85 mmHg and the patient stated an improvement of vision. BCVA in the right eye was 20/63, in the left eye 20/80. On the ocular fundus we recorded a regression of the finding – in the macula of the right eye the edema had virtually receded and the size and scope of intraretinal haemorrhage had been reduced bilaterally (fig. 6). The OCT finding on the central region confirmed regression of macular edema (fig. 7).

## CASE REPORT 3

The patient, a 40 year old man, was sent to the Department of Ophthalmology at the University Hospital Hradec Králové for examination of the ocular fundus following one week of antihypertensive therapy. From the anamnesis it ensued that for approximately one month the patient had noticed respiratory difficulties, a dry cough and tightening of the chest. At the Internal Clinic at the University Hospi-

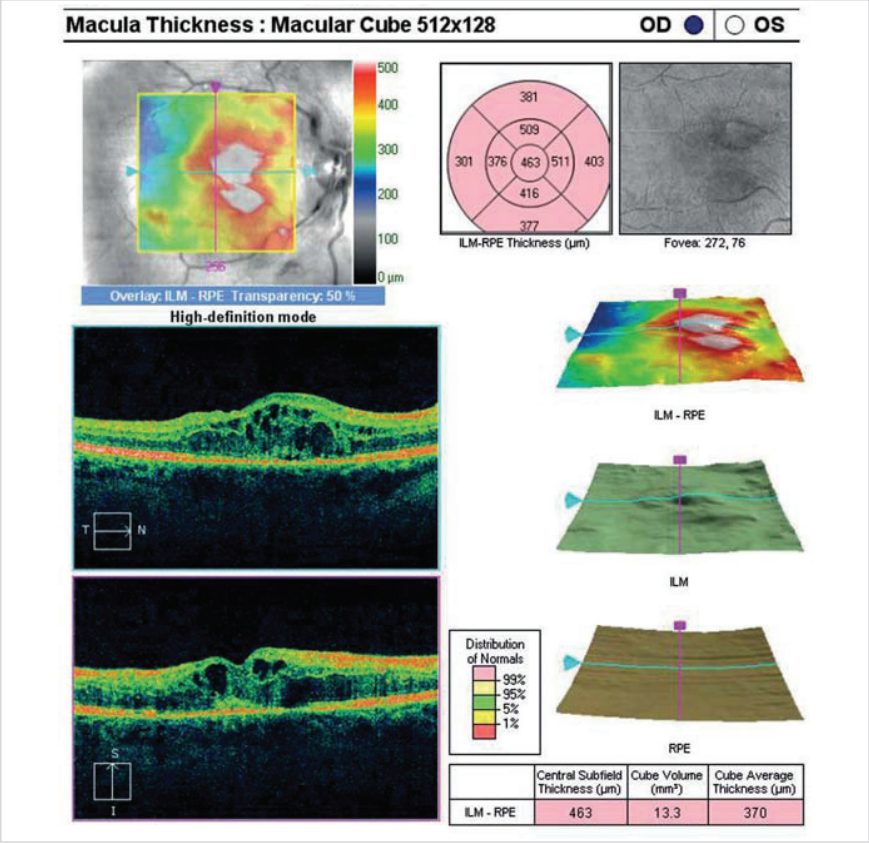


**Fig. 5** OCT of central region of right eye. Cystic neuroretinal edema.

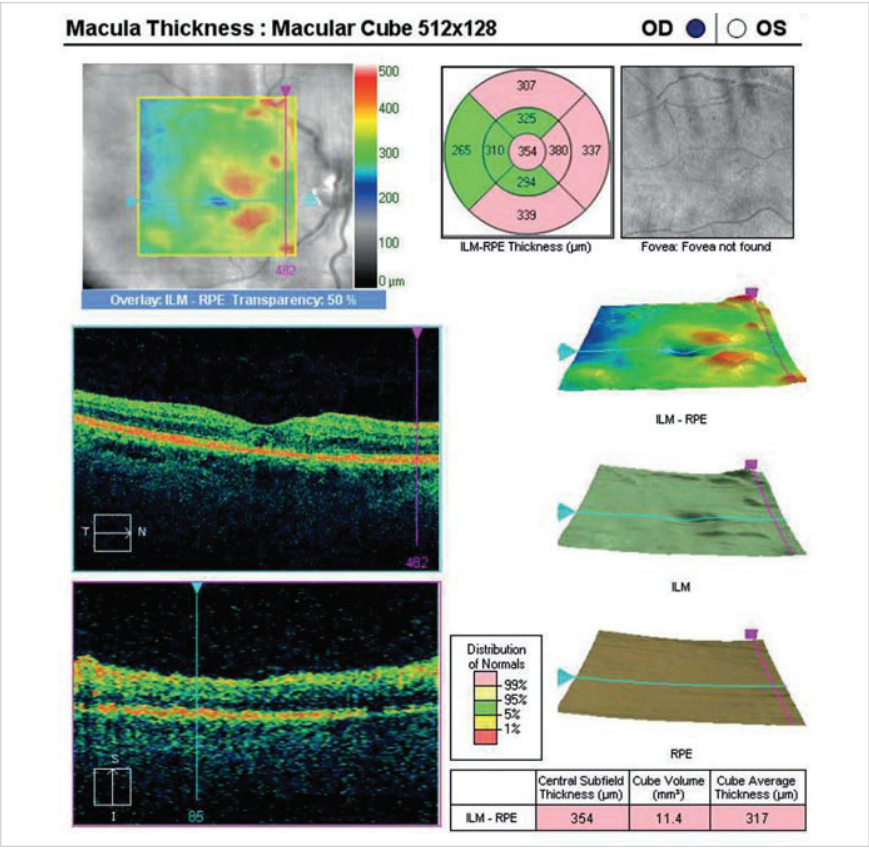


**Fig. 7** OCT of central region of right eye. Regression of neuroretinal edema, foveolar depression formed.

**Fig. 6** Right eye. Regression of finding, edema virtually receded in central region, size and scope of intraretinal haemorrhage decreasing

tal Hradec Králové he was examined with the following conclusion: malignant hypertension with blood pressure values of 250/170 mmHg. An x-ray examination of the chest showed an enlargement of the width of the heart shadow, finding of engorgement and exudation in the left lung. Due to the above complaints, the following therapy was initiated: Bisoprolol 2.5 mg 1-0-0, Verospiron 25 mg 1-0-0 (spi-

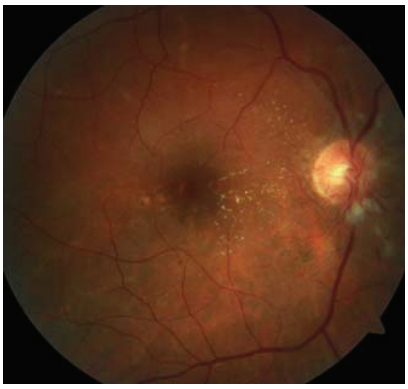

**Fig. 8** Right eye. Pronounced hypertonic retinopathy, stage 3 according to Keith. Dominant accentuation of capillary network on papilla.

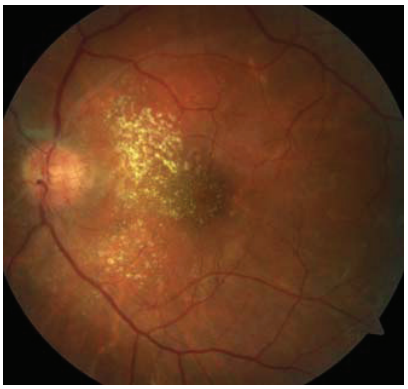

**Fig. 9** Analogous finding on ocular fundus of left eye with more pronounced exudation in macula.

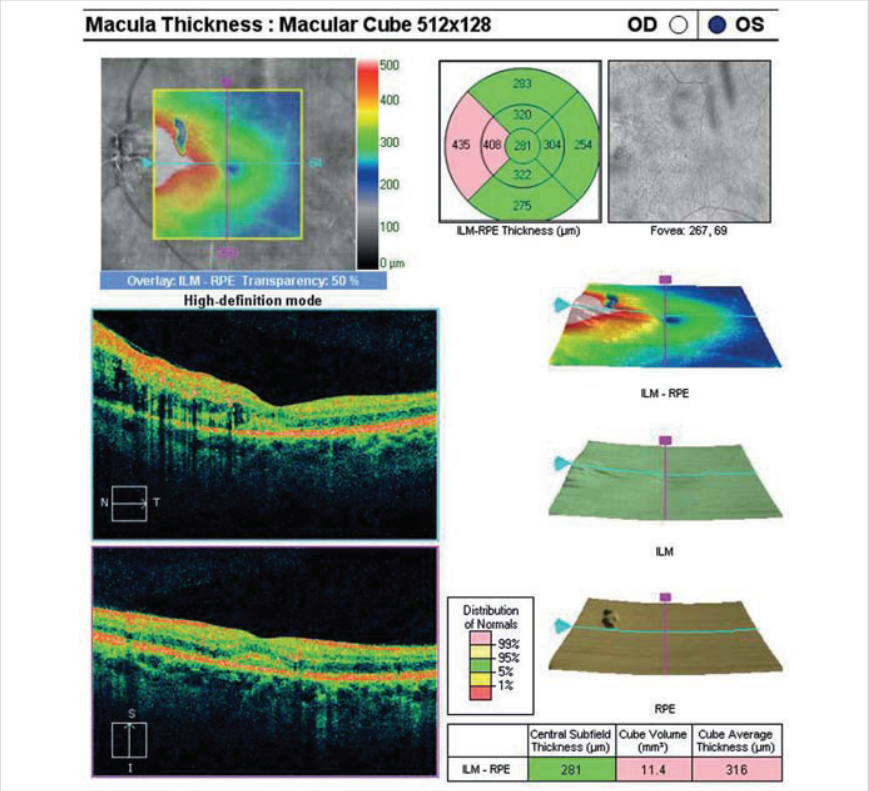


**Fig. 10** OCT of central region of left eye. Neuroretinal edema, which continues in the direction towards the disc of the optic nerve.

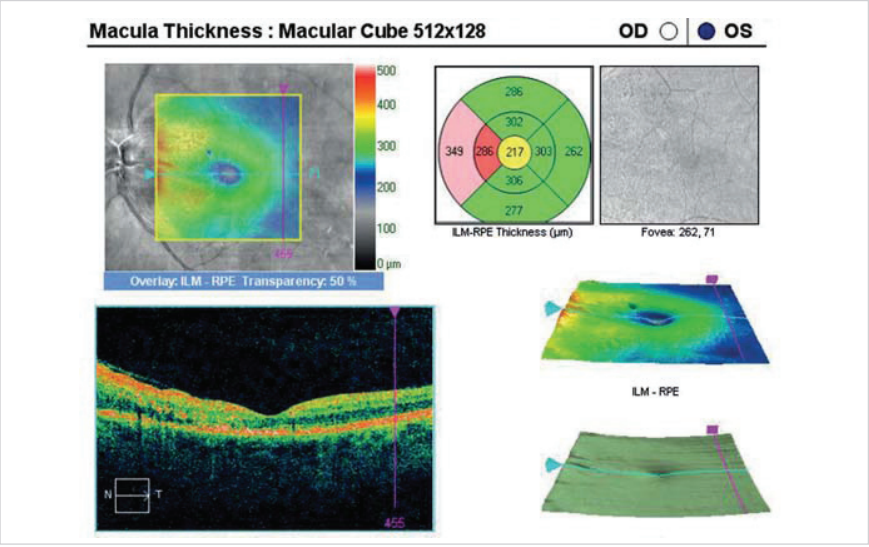


**Fig. 13** OCT of central region of left eye. Regression of neuroretinal edema.

**Table 1** Keith-Wagener-Barker classification.

| | |
|---|---|
| Level 1 | Slight constriction, sclerosis and tortuosity of arterioles |
| Level 2 | Medium to pronounced constriction of arterioles |
| | Disappearance of ophthalmoscopic reflexes |
| | Positive phenomenon of crossing |
| Level 3 | Stenosis of retinal arterioles and focal constriction of capillaries |
| | Retinal swelling |
| | Cotton wool spots |
| | Retinal haemorrhage |
| Level 4 | All features of group 3 plus edema of papilla of optic nerve |

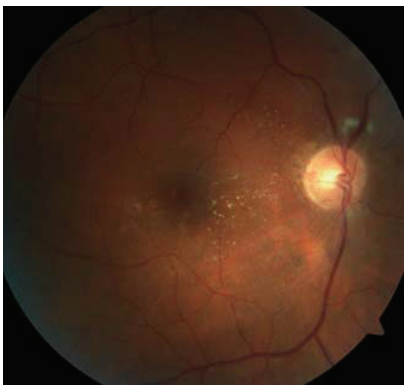

**Fig. 11** Right eye. Improvement of condition following compensation of blood pressure.

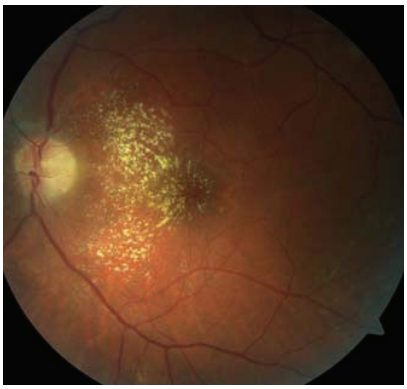

**Fig. 12** Left eye. Improvement of condition.

ronolactone), Cardilopin 10 mg -0-0 (amlodipine). Of ocular complaints the patient perceived deterioration of visual acuity in the left eye persisting for one month. Initial BCVA in the right eye was 20/20 in the left eye 20/40. At our examination blood pressure was already compensated – 130/85 mmHg. The finding on the anterior segment of the eye was bilaterally commensurate to age. Accentuation of the capillary network on the papillas dominated on the ocular fundus, with isolated peripapillary cotton wool spots. In the capillaries we observed pronounced sclerotic changes, arteries with an appearance of silver wire, veins wide with pronounced phenomena of crossing. In the central region there were evident hard exudates and splattered haemorrhages (fig. 8, 9). Optical coherence tomography of the central region of the left eye showed neuroretinal edema in the direction from the papilla to the macula (fig. 10). In the right eye the finding on OCT of the central region was commensurate to age. At a follow-up examination after one month, BCVA was unchanged, but there was a visible improvement of the objective condition on the ocular fundus. The capillary network on the

papillas was no longer so pronounced, there was a bilateral reduction in the size and scope of the cotton wool spots and intraretinal haemorrhage, although hard exudates were still evident. At this follow-up examination, blood pressure was compensated to values of 125/80 mmHg. On OCT of the left eye we observe a regression of neuroretinal edema (fig. 13).

## DISCUSSION

According to the level of BP at the first measurement (without medication), we differentiate between 1st degree arterial hypertension (slight hypertension) with BP values of 140-159/90-99 mmHg, 2nd degree hypertension (medium-severe) with BP 160/179/100-109 mmHg and 3rd degree hypertension (severe arterial hypertension) with BP values of > 180/110 mmHg (12). In our case we recorded 3rd degree arterial hypertension in all patients.

Arterial hypertension may be the source of numerous ocular complications. Some are entirely without symptoms and are generally determined by chance at a routine eye examination, others cause mild to severe loss of vision of the afflicted eye. The first and broadest classification of hypertonic changes on the ocular fundus is the classification according to Keith (6) (table 1). In the cases we present, we recorded severe changes on the ocular fundus bilaterally in all patients, according to Keith degree 3-4.

With successful treatment of hypertension, changes on the retina and on the disc of the optic nerve can recede completely, however, arterial constriction and the phenomenon of crossing are irreversible (10). In our cases numbers 2 and 3 also, at the planned follow-up following compensation of blood pressure vision improved and there was a partial regression of pathological changes on the ocular fundus.

As regards local ocular therapy, in the case of malignant hypertension with pronounced papillary edema, the effectiveness of intravitreal injection of VEGF (Vascular Endothelial Growth Factor) inhibitors is demonstrated (1). In the patients we described, this option was not chosen due to the absence of pronounced papillary edema and the regression of the pathological changes following compensation of arterial hypertension.

## CONCLUSION

In certain cases, ocular complaints are the first sign of decompensation of arterial hypertension. The treatment of arterial hypertension requires good co-operation between the ophthalmologist and the internist. With successful treatment of hypertension, changes on the retina and on the disc of the optic nerve can regress completely. In the cases we present, following compensation of blood pressure there was an improvement of vision and the objective finding on the ocular fundus.

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CASE REPORT

# The Use of Anti-VEGF Preparations and PDT in the Treatment of Retinal Juxtapapillary Hemangioma – A Case Report

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## SUMMARY

**Aim:** The aim of this paper is to present clinical experience with the therapy of retinal juxtapapillary hemangioma using the intravitreal application of anti-VEGF substance (bevacizumab) and photodynamic therapy (PDT) with verteporfine (Visudyne).
**Material and methods:** The authors present a case of a 34 years old male patient with diagnosed retinal hemangioma localized on the optic disc. Subjectively, the patient noticed decrease of vision, and during the clinical examination, the edema in the macula region spreading from the hemangioma with hard exsudates was found; the best-corrected visual acuity (BCVA) was 4/20 (0.2).
**Results:** First, the patient was treated by intravitreal applications of bevacizumab; after the first application, the edema from the macula subsided, and the best-corrected visual acuity improved to 4/12 (0.33). After one month of the first application, a recurrence of the edema occurred and other two injections of bevacizumab were applied; despite this treatment, further worsening of the exsudation from the hemangioma and worsening of the BCVA to 4/32 (0.125) occurred. Subsequently, one session of photodynamic therapy with verteporfine was held. After this therapy, the finding on the posterior ocular pole was stabilized; the BCVA was 4/40 (0.1). Even one year after the PDT therapy, no recurrence was present.
**Conclusion:** According to our experience, the PDT with Visudyne appears as promising therapy method of juxtapapillary capillary hemangiomas. The PDT decreases the leaking of the fluid from hemangioma and decreases the size of hemangioma.

**Key words: Capillary hemangioma, PDT, juxtapapillary hemangioma, bevazicumab, verteporfine, von Hippel – Lindau disease**

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## INTRODUCTION

Retinal hemangioma is a benign vascular tumour originating from the capillaries of the retina or the optic nerve. In the English speaking literature, the synonym of retinal hemangioblastoma is sometimes used. It occurs in isolated form (unilaterally) or numerously as a part of von Hippel Lindau syndrome. It usually occurs in patients aged 15-35 years, the median age of the incidence of hemangioma as a part of Hippel Lindau syndrome is 18 years, in the case of isolated lesions 31 years (3).
The tumour is composed of vascular structures similar to capillaries, as a result the term capillary is used. Hemangioma usually has an endophytic growth. It is characterised by an oval shape, well defined and dilated, a tortuous feeding artery and drainage vein. It is frequently linked to the presence of retinal swelling, serious elevation of the retina or the incidence of hard exudates. It may be localised to the retina or on the papilla of the optic nerve. Less frequent is exophytic growth of a hemangioma. In this case a small, well defined placoid juxtapapillary lesion is evident, with dilated blood vessels. On fluorescence angiography it is possible to observe early hyperfluorescence of the lesion, with later infiltration (3, 9).

## CASE REPORT

A 32 year old man reported to the outpatient department of our clinic due to a deterioration of vision in the right eye persisting for one month. He had been treated generally for hypertension, and had blood pressure compensated on established medication of betaxolol hydrochloride 20/ mg per day. At an objective examination, visual acuity (VA) in the right eye with correction was 0.75 Dsf 4/20, in the left eye vision with -1.0 Dsf 4/4. Intraocular pressure was within the norm, the finding on the anterior segment was physiological. Following the induction of artificial mydriasis, a vascularised projecting formation with a papillary diameter (PD) of 1.5 was visible on the papilla of the optic nerve on the fundus of the right eye, with edema with hard exudates extending from the vascularised lesion to the macula (fig. 1, 2, 3). The finding on the fundus of the left eye was physiological. In order to confirm the diagnosis we performed fluorescence angiography (fig. 4). The deposit on the papilla was saturated with a contrast substance from the early arterial phase, infiltration from the lesion into the surrounding area was progressively evident. We diagnosed the lesion as a solitary juxtapapillary capillary hemangioma. In order to exclude the possibility of hemangiomas in the central nervous system and kidneys, we performed magnetic resonance imaging of the brain and a

sonographic examination of the kidneys, the finding was negative.
With regard to the size and localisation of the lesion on the papilla of the optic nerve, we did not indicate the performance of laser photocoagulation, crystallisation or brachytherapy. After evaluating the finding and studying the published works, we decided to embark upon intravitreal administration of bevacizumab (Avastin, Roche Pharma AG). We applied 2.5 mg of bevacizumab intravitreally with aseptic kautel in the operating theatre. One week after the application there was a perceptible improvement of best corrected visual acuity (BCVA) in the right eye to 4/12. On the fundus we observed a distinct regression of the edema from the macula, on optical coherence tomography (OCT) there was a visible foveolar depression (fig. 5, 6). One month after the first application there was a recurrence of edema (fig. 7, 8), and with regard to the first good response to treatment, a further 2 injections of bevacizumab were applied (fig. 9, 10). Even despite this treatment there was a further exudation from the hemangioma and a deterioration of BCVA in the right eye to 4/32. On the fundus of the right eye

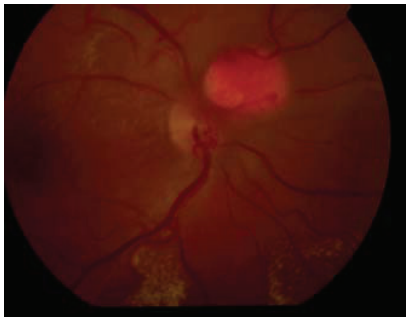


**Fig. 1**

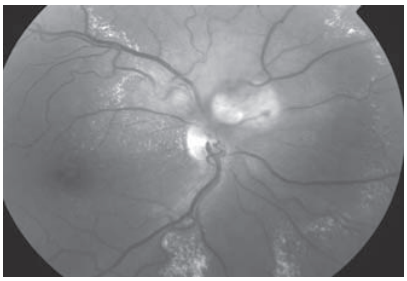


**Fig. 2**

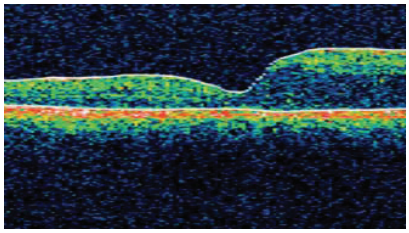


**Fig. 3**

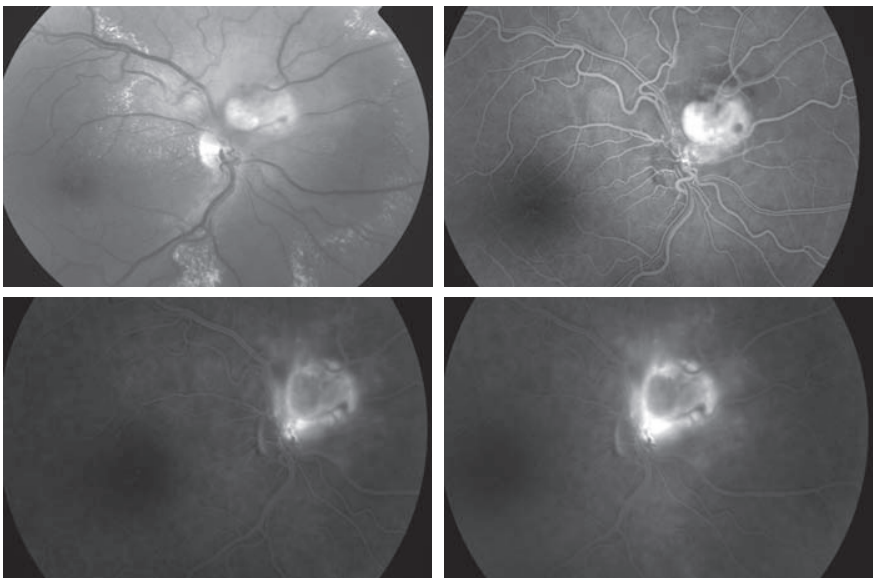
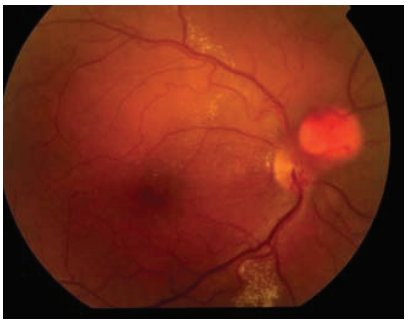


**Fig. 4**

we again observed haemorrhages in the surrounding area of the hemangioma (fig. 11). The edema encroached into the region of the macula, and from the beginning of treatment hard exudates accrued, primarily in the lower half of the macula. Macular edema was visible upon OCT (fig. 12). With regard to the unsuccessful therapy using a substance against vascular endothelial growth factor (anti-VEGF), we decided to embark upon the performance of photodynamic therapy (PDT) with Visudyne in a standard regimen (fig. 13 a, b), BCVA in the right eye on the day of performance of PDT was 4/40sl. At a follow-up examination one month after PDT, there was an evident pronounced reduction in the substance of the capillary hemangioma, haemorrhage persisted around the papilla, and we also observed a reduction of exudation from the hemangioma (fig. 14), on OCT foveolar depression was perceptible (fig. 15), BCVA in the right eye was 4/40. At a follow-up examination one year after the performance of PDT there was an evident reduced mass of the original capillary hemangioma on the fundus, without accompanying haemorrhages or edema, hard exudates persisted underneath the macula (fig. 16). On OCT a foveolar depression had formed on the macula (fig. 17a). On a scan leading through the reduced capillary hemangioma there is no evident fluid above the mass of the original tumour (fig. 17b). On fluorescence angiography we observed a pronounced reduction in the substance of the capillary hemangioma, only in the later phases there is evident mild hyperfluorescence (fig. 18). This finding persisted also for a year and a half following photodynamic therapy with Visudyne. There was also an evident further reduction in the mass of the hemangioma (fig. 19 a, b).



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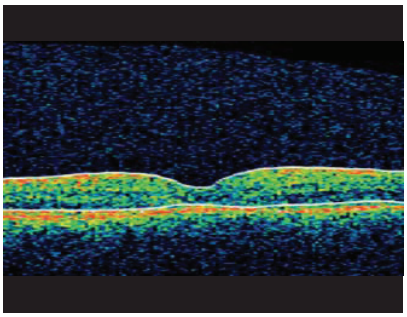

**Fig. 6**

**Fig. 7**

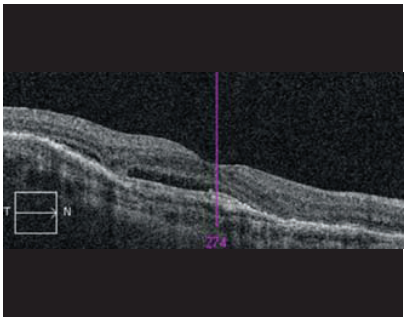

Fig. 8

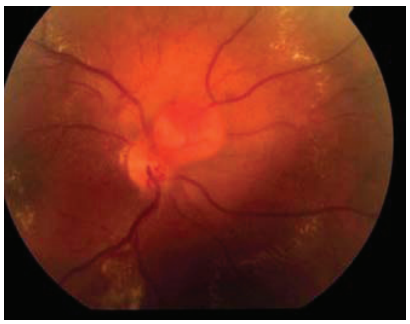

Fig. 9

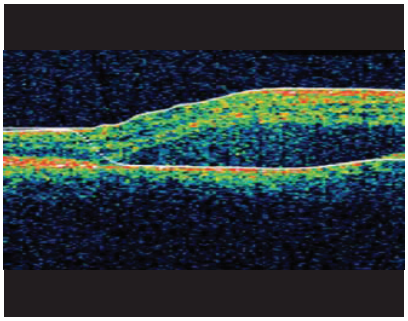

Fig. 10

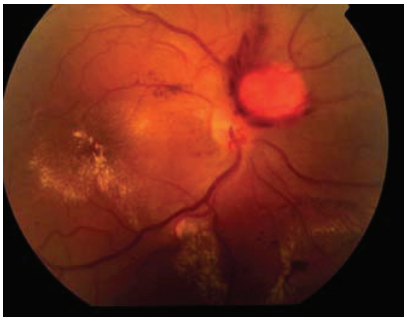

Fig. 11

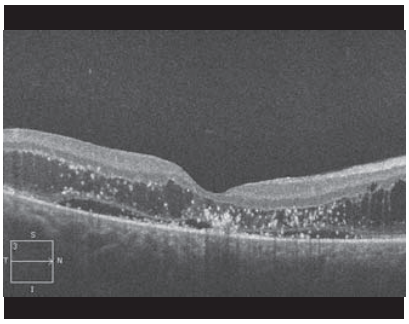

Fig. 12

Fig. 13

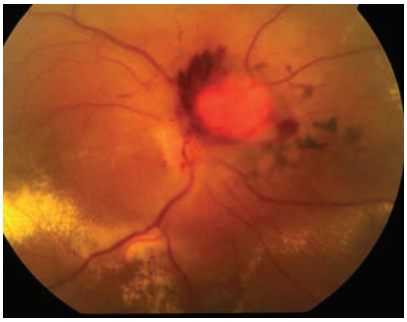

Fig. 14

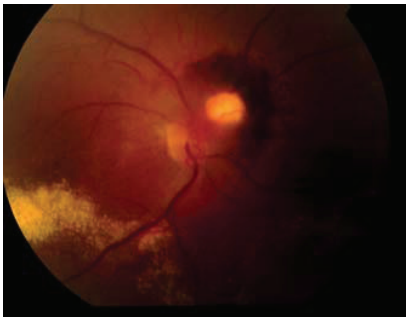

Fig. 15

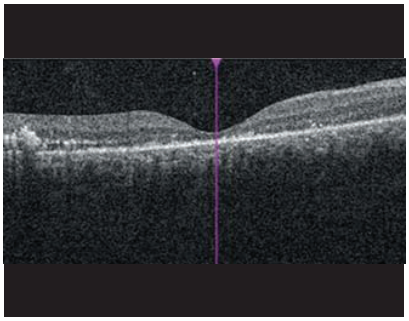

Fig. 16

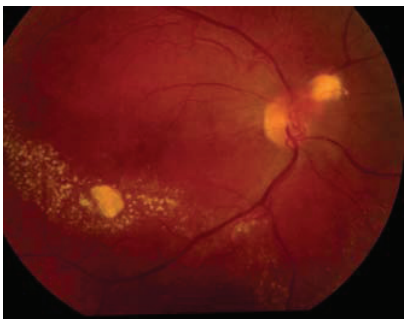

Fig. 17

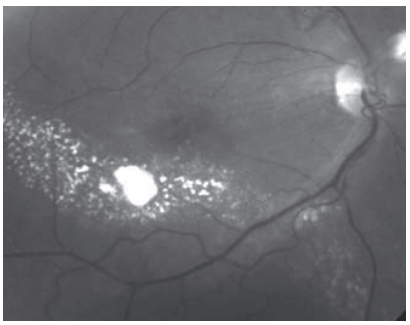

Fig. 18

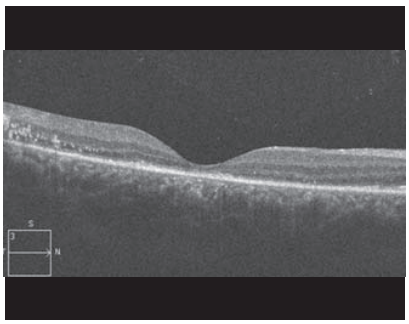

Fig. 19

## DISCUSSION

The spontaneous course of capillary retinal hemangioma is usually progressive and leads to a pronounced deterioration of visual acuity. The study by McGabe et al., who observed the natural course of the disease in 72 patients with capillary juxtapapillary hemangioma, describes vision worse than 20/40 in 65% of patients after 5 years of observation (5). In the Czech literature, the issue of therapy of Hippel Lindau syndrome is dealt with by Karel. In his study he published his experiences with laser photocoagulation in the case of a hemangioma lying between the macula and the equator (4).

In general it is recommended to commence therapeutic intervention at the moment when the hemangioma becomes symptomatic (i.e. when exudation or subretinal fluid impairs visual acuity) (9). In the case of small symptomatic lesions, laser photocoagulation is recommended, first of all coagulation of the "feeding vessels", followed by coagulation of the lesion by beams with low energy and longer duration in several sessions. For larger lesions in the periphery, cryotherapy is recommended, in the case of enormous lesions it is possible also to use brachytherapy (10). Pars plana vitrectomy (PPV) with endolaser photocoagulation is reserved for hemangiomas combined with non-resorbable haemophthalmos, with epiretinal

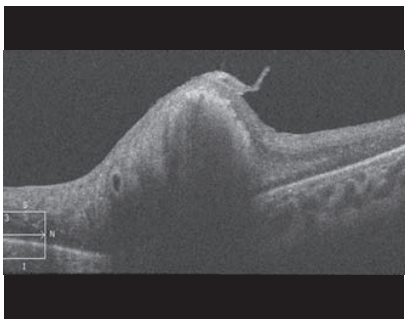

**Fig. 8**

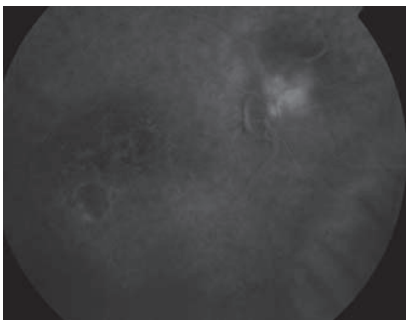

**Fig. 9**

**Fig. 10**

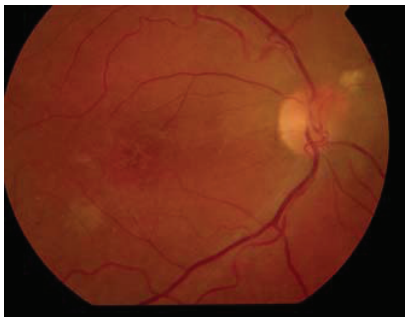

**Fig. 8**

fibrosis or tractional retinal detachment (3). Therapy of juxtapapillary hemangiomas is one of the most complex and high risk procedures. The structure of the lesion lying inside the retina and the nerve fibres, as well as the absence of retinal pigment epithelium as the primary absorber, means a high risk of damage to the nerve structures upon laser therapy (9). With regard to the fact that the above-stated therapies have a range of adverse effects, studies dealing with the systematic application of bevacizumab have been published in recent years (11, 12). In both cases, systematic application did not produce a good therapeutic effect. Further studies focused on intravitreal application of bevacizumab or PDT (6, 8, 13). A small study on the use of pegaptanib is published in the literature. In the patients in this study there was a reduction of edema and resorption of hard exudates, but therapy did not lead to a reduction of the hemangioma (2). Wackenagel et al. published a study with systematic administration of bevacizumab to a patient with retinal hemangioma in a dose of 5 mg/kg every second week. After 2 months of therapy there was an improvement in visual acuity and a regression of macular edema. However, after the 7th dose a new hemangioma formed, and as a result the therapy was discontinued (12).

Photodynamic therapy with Visudyne is approved for the treatment of classic subfoveolar choroidal neovascular membrane (CNV) in wet form age-related macular degeneration, and also for myopic and post-inflammatory classic CNV. Verteporfine is administered into the vein in a dose of 6 mg/m2. 15 minutes after the commencement of infusion with verteporfine, the afflicted area is treated by laser at a wavelength of 692 nm for a period of 83 seconds (in a dose of 600 mW/cm2. The size of the beam is chosen according to the size of the lesion and a safety margin of 1000 μm is added (7). Mennel et al. applied 5 injections of bevacizumab to their patient, PDT was performed 8 days after the first application of bevacizumab. 14 days after the performance of PDT they describe a pronounced improvement of macular edema. Due to persisting infiltration of fluid from the hemangioma, a second PDT was performed after 2 months. After the completion of treatment, over the course of a one-year observation period there was a complete resorption of hard exudates and intra and subretinal fluid. In order to minimise the vaso-occulsive effect, Mennel did not apply laser to the part of the hemangioma on the papilla of the optic nerve (6). Von Buklow et al. observed an unsuccessful therapeutic combination of triamcinolone and PDT in their patient. Following the application of 2 injections of triamcinolone and one session of PDT there was an increase in exudation from the capillary hemangioma. For this reason the patient was administered bevacizumab intravenously in a dose of 6 mg/kg in 6 cycles over 14 days. Following this treatment there was only a transitory reduction in the amount of fluid on the retina, over the course of one-year observation there was again a growth of edema and a progression of exudative retinal detachment. The patient refused further treatment (11).

Positive experiences with the thrombolisation of newly-formed vessels and the result of this, with inducement of regression of choroidal hemangiomas, were published in the study by Schmidt-Erfurth et al. (8). The same author published the successful use of PDT in retinal juxtapapillary hemangioma on a group of 5 patients (9). In all patients there was a regression of macular edema, in 3 patients a deterioration of VA by 1, 3 and 10 rows was observed over a one-year observation period. Deterioration by 10 rows of ETDRS optotypes was observed in a patient with initial vision of 20/40, in whom there was a sudden decrease in visual acuity 2 hours after the performance of PDT as a consequence of haemorrhage into the vitreous body. Within 6 weeks there was a resorption of hemophthalmos and there was a perceptible increase in peripapillary exudation, and as a result a second session of PDT was performed. Subsequently serious retinal ischemia occurred, with damage to the optic nerve (verified in visual evoked potentials). In all 5 patients the energy of PDT was increased ti 100 J/cm2. The number of PDT sessions was 1 to 3 (9). Positive experiences with bevacizumab and PDT in therapy have been published by Ziemmsen et al. They extended the period of laser application to 166 seconds as against the standard time of 83 seconds (13). Closure of the vascular structures of the hemangioma, even if transitory, was demonstrated in the work by Bakri et al. The author applied PDT twice at an interval of 5 weeks (1) in a standard regime to an 11 year old boy.

Clinical experiments demonstrate that the effect of PDT resides in a remodelling of the vascular wall and in a reduction of permeability rather than in permanent occlusion (9).

## CONCLUSION

Photodynamic therapy (PDT) with Visudyne is capable of successfully reducing the size of juxtapapillary hemangioma and its activity. According to our experiences, a combination of PDT with anti-VEGF substances appears to be promising, leading to a sizeable reduction in the activity of the tumour, but this alone does not have the potential to eliminate activity.

## LITERATURE


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CASE REPORT

# Frosted Branch Angiitis Syndrome

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## SUMMARY

The authors present a case report of a 20-year-old patient with an atypical clinical picture of bilateral vasculitis associated with bilateral macular oedema and decrease in visual acuity. On basis of the clinical picture, frosted branch angiitis was diagnosed. The patient was instructed to continue the broad-spectrum antibiotic therapy prescribed by an ophthalmic practitioner of the appropriate catchment area. The visual acuity progressively improved and after application of systemic corticosteroid therapy the patient's health state improved completely.
According to the author's knowledge, this is the first diagnosed case of frosted branch angiitis in the Slovak Republic.

**Key words: frosted branch angiitis, vasculitis, angiitis**

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## INTRODUCTION

Bilateral vasculitis in a 6 year old Japanese boy was described by Ito et al. in 1976. The clinical picture of vasculitis was reminiscent of frosted tree branches, and as a result the authors used the name frosted branch angiitis (1). This pathology has not been described to date in Slovakia. In the Czech Republic Říhová et al. first described this pathology in 2004, and proposed the name frosted branches of retinal blood vessels syndrome (2).
Frosted branch angiitis syndrome is clinically manifested as anterior uveitis, vitritis and vasculitis. The branches of the retinal blood vessels are coated with an inflammatory infiltrate from the disc of the optic nerve (DON) to the periphery, with veins afflicted more frequently than arteries. Upon examination by fluorescence angiography (FAG), symptoms of later infiltration from blood vessels are present, but without symptoms of vascular occlusion. In the later stages, geographic atrophic lesions have been observed in the periphery of the retina in some patients. The majority of authors state a very good therapeutic effect of generally administered corticosteroids. Frosted branch angiitis syndrome most frequently afflicts young and healthy individuals. Some of these have overcome influenza a number of weeks before the ocular complaints (1).
Kleiner (1997) noted the fact that similar ocular findings as in frosted branch angiitis syndrome may occur also in patients with a systemic or hematologic pathology, in immunocompetent or immunodeficient individuals in connection with infection, most frequently viral (3).
If infiltration of the blood vessels is caused by malignant cells upon lymphoma or leukaemia, this represents a syndrome similar to frosted branches. If the finding is a manifestation of immune complex vasculitis caused by a viral infection or autoimmune disease, the pathology is referred to as secondary vasculitis with frosted branches. If the etiological agent is not demonstrated, this represents acute idiopathic vasculitis with frosted branches (4). In this case, vasculitis is caused by immune processes triggered by as yet unclear stimuli.
In our study we present a case report of a patient with a clinical picture of frosted branch angiitis syndrome.

## CASE REPORT

A healthy 20 year old man overcame a viral pathology of the upper respiratory tracts in mid-December 2008. 4 weeks later, in mid-January 2009, he was examined due to bilateral deterioration of vision persisting for 3 days at the outpatient clinic of the district ophthalmologist. The district ophthalmologist determined a working diagnosis of bilateral diffuse retinitis of unclear etiology, and recommended the following therapy for the patient: generally Rovamycin 3 MIU, 1 tablet every 12 hours, Tebokan 1 tablet 3x daily, and Unicophlen drops (gtt.) 5x daily applied locally to both eyes. Due to the unusual ocular finding and diagnostic inconclusiveness, the patient was advised to attend an examination at the Department of Ophthalmology of the Jesenius Faculty of Medicine of Comenius University and the University Hospital in Martin the next day.
The patient was examined in the outpatient department of the Department of Ophthalmology of the Jesenius Faculty of Medicine of Comenius University and the University Hospital in Martin on 16 January.
The personal anamnesis of the 20 year old man was negative, except for the current deterioration of vision and the virus 4 weeks previously. As a student of the military academy, he had regularly undergone health checks (including ocular examination) before contracting the disease, without a pathological finding. We did not record any more serious ocular or systemic pathologies in the family anamnesis.
From an ophthalmological perspective, the patient had not experienced any ocular complaints to date. Upon the first examination at our outpatient clinic, natural vision was bilaterally 6/38, best corrected visual acuity (BCVA) bilaterally 6/18. Intraocular pressure was within the norm (12 and 13 mmHg). There were mild sym-

**Fig. 1** Right eye of patient upon admittance
Inflammatory infiltrates around the branches of the retinal blood vessels, DON with slightly blurred boundaries at the upper and lower pole. BCVA: 6/18.

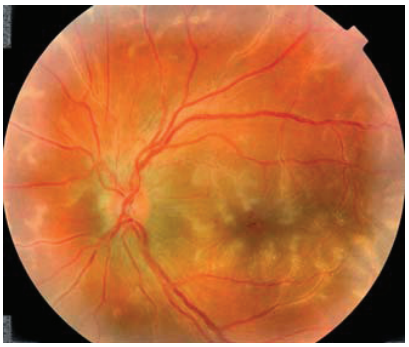

**Fig. 2** Left eye of patient upon admittance
Inflammatory infiltrates around the branches of the retinal blood vessels, DON with slightly blurred boundaries at the upper and lower pole, with retinal haemorrhages in the centre of the macular region. BCVA: 6/18.

ptoms of anterior uveitis bilaterally in the anterior segment (minor non-granulomatous precipitates on the corneal endothelium, cells in the anterior chamber), the pupils were loose, without posterior synechiae, the lenses clear. The vitreous body was slightly turbid, DON edematous, the macular region edematous, inflammatory infiltrates dominated in the clinical picture around the branches of the retinal blood vessels, accompanied by retinal haemorrhages (fig. 1, 2).
Upon examination by optical coherence tomography (OCT) (Stratus, Zeiss), the foveolar contour was preserved, the neuroretina in the region of the fovea was coarsened, elevated, with present non-reflective cystoid cavities. Thickness of foveola in the right eye was 507 µm, in the left eye 552 µm (fig. 3).
In the examination we determined a working diagnosis of frosted branch angiitis syndrome, and the patient was hospitalised. We focused further laboratory and general examinations on determining the specific type of the syndrome and excluding or confirming the infectious etiology of vasculitis, or its connection with a haematological or other general pathology.
On the basis of the fact that the infiltrates around the branches of the retinal blood vessels did not appear unilaterally but bilaterally, and the examination of the blood count and differential blood count was within the framework

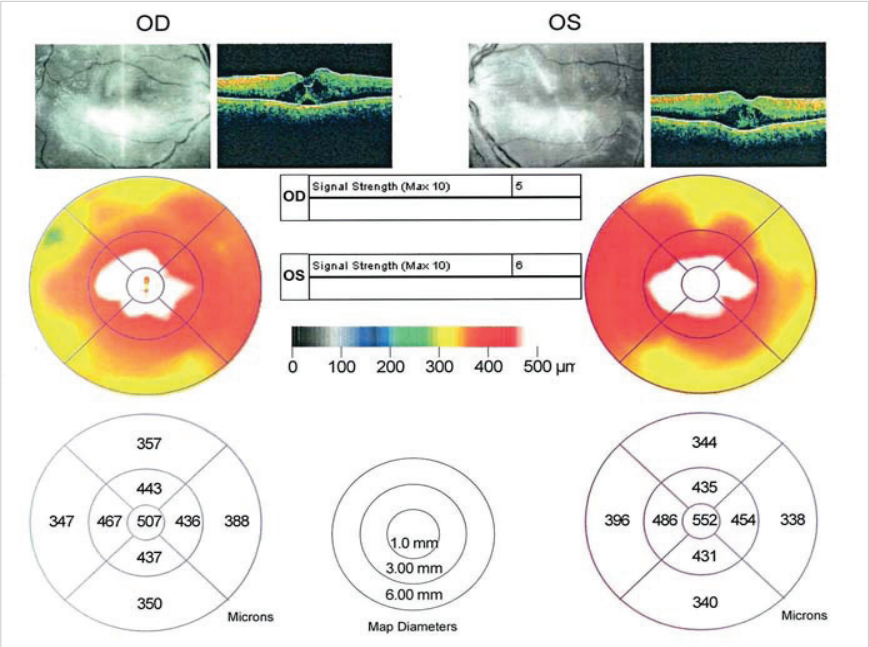


**Fig. 3** OCT finding of patient upon admittance
Preserved foveolar contour, neuroretina elevated in the region of the fovea, with cystoid non-reflective cavities. Thickness of foveola in right eye 507 µm, in left eye 552 µm.

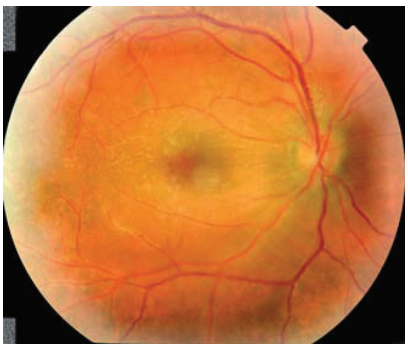

**Fig. 4** Right eye of patient on 4th day of hospitalisation
Inflammatory infiltrates reduced, haemorrhages partially reabsorbed

**Fig. 5** Left eye of patient on 4th day of hospitalisation
Inflammatory infiltrates almost entirely reabsorbed, haemorrhages partially reabsorbed

of physiological values, we excluded infiltration of the blood vessels with malignant cells on the day of admittance. This did not concern a haematological pathology, but immune complex vasculitis, without a demonstrated etiological agent. Despite the fact that the majority of authors (1, 3, 5, 8, 10, 11, 12) state an improvement of the clinical picture and vision in this clinical unit following periocularly and generally administered corticoids, due to the potential influence on the results of flow cytometry, we did not apply corticotherapy until the 4th day of hospitalisation (upon an improvement of the finding also without corticotherapy).
Upon admittance we added Ibalgin 400 mg 1 tablet 3x daily and Ascorutin 2 drg. 3x daily to the treatment stipulated by the district ophthalmologist (Rovamycin 3 MIU, 1 tablet every 12 hours, Tebokan 1 tablet 3x daily, Unicophlen gtt. 5x daily applied locally to both eyes). Within the first days of observation, best corrected visual acuity and the finding on the ocular fundus improved markedly. On the 4th day of hospitalisation, BCVA had improved bilaterally to 6/12 before

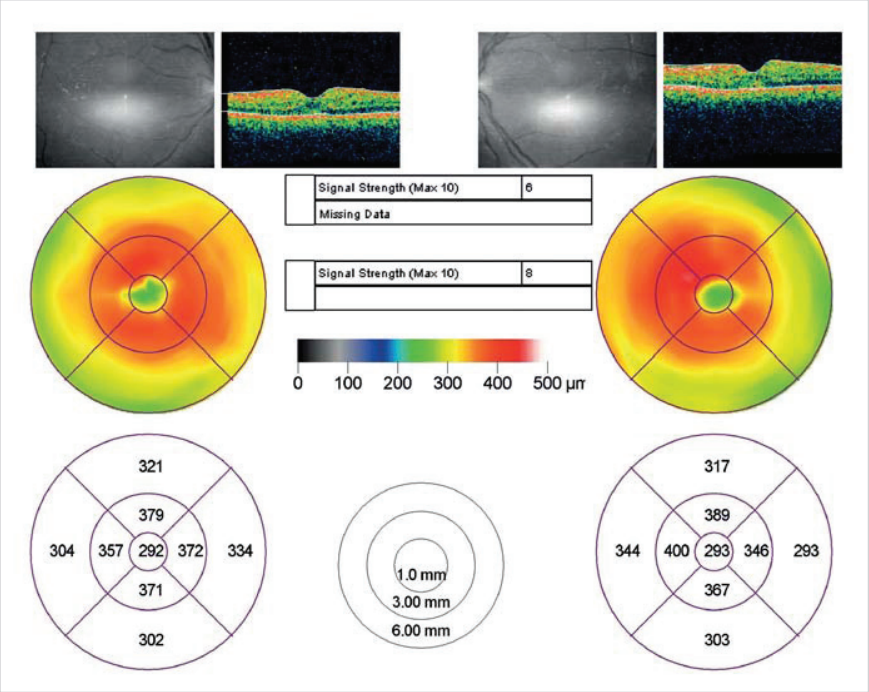


**Fig. 6** OCT images of patient on 4th day of hospitalisation
Decrease in edema in foveola in right eye by 215 µm, in left eye by 259 µm

the application of corticotherapy, the inflammatory infiltrates had virtually disappeared, and the haemorrhages had been partially reabsorbed (fig. 4, 5). Edema in the foveola of the right eye had decreased by 215 µm, in the left eye by 259 µm (fig. 6).
Despite the partial improvement in the ocular finding, we implemented the planned commencement of corticotherapy following the taking of a blood samples for examinations of flow cytometry and phagocytic activity on the 4th day of hospitalisation. Over the course of three days, we intravenously applied Solumedrol in a dose of 250 mg/day. In corticotherapy we continued with Prednisone 1 mg/kg/day, following adjustment of the ocular finding we began to reduce the dose of Prednisone on the 7th day by 10 mg every 3 days, to a maintenance dose of 10 mg every second day, generally for a period of 2 months. During therapy by corticoids we did not record any secondary adverse effects or complications.
The result of electrophoresis of proteins in serum, the immunochemical examination, examination of flow cytometry, phagocytic activity and the quantiferon test excluded immune disorder. Rheumatoid factor, anti-nuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA), serological examination of antibodies against borrelias, mycoplasmas, yersinias, herpes simplex virus (HSV), herpes zoster virus (HZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), rubella and VDRL were negative.

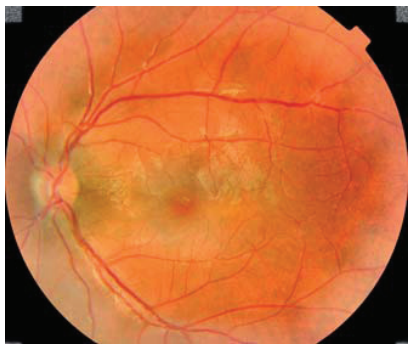

**Fig. 8** Left eye of patient at first follow-up examination after discharging DON bordered, pink, without edema, inflammatory exudates to haemorrhages completely disappeared, in macula frilling of lamina limitans interna, slight atrophy of RPE in foveolar region.

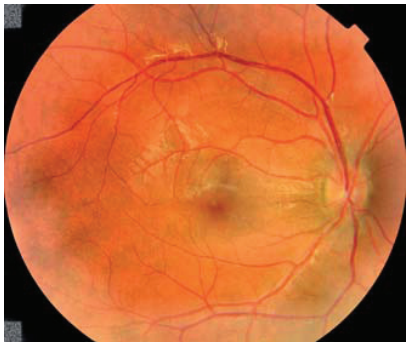

**Fig. 7** Right eye of patient at first follow-up examination after discharging DON bordered, pink, without edema, inflammatory exudates to haemorrhages completely disappeared, frilling of lamina limitans interna, slight

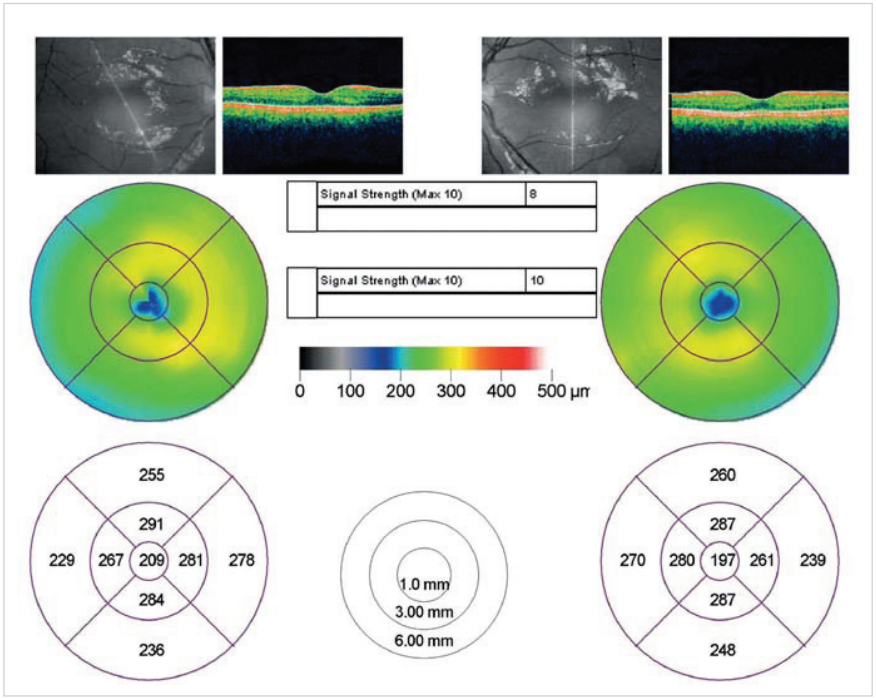


**Fig. 9** OCT finding of patient at first follow-up examination after discharging
Physiological finding, neuroretina without edema, without cystoid non-reflective cavities or microcystic remodelling

Within the framework of differential diagnostics to eliminate sarcoidosis performed by X-ray examination of the chest, pneumological examination and examination of cellular immune status from bronchoalveolar lavage on the recommendation of a pneumologist, the results were however also negative.
Positive findings were antibodies of class IgA and IgG against Chlamydia trachomatis. As a result an infectologist was consulted, who despite the completion of the course of Rovamycin once more recommended re-treatment of the patient with Deoxymykoin in a dose of 100 mg 2x daily.
At the first follow-up examination after discharging on 9 February 2009, BCVA was 6/4 bilaterally, the anterior segment was physiological, without symptoms of inflammation, the vitreous body clear, DON bordered, pink, retinal blood vessels were without symptoms of vasculitis, exudates completely reabsorbed, with only slight atrophy of the retinal pigment epithelium (RPE) in the foveolar region, in the entire macula frilled lamina limitans interna, other finding without pathology, haemorrhages completely reabsorbed (fig. 7, 8). According to the OCT images foveolar contour is present, cystoid non-reflective cavities are not present, neither is microcystic remodelling of the neuroretina (fig. 9). At a further follow-up examination after six months the patient is subjectively without ocular complaints, corrected visual acuity bilaterally 6/4, local finding without change.

## DISCUSSION

Frosted branch angiitis syndrome was first observed in Japan in 1976 (1). The largest proportion of patients is amongst the Japanese (75%). Until 1988 no patient outside Japan had been diagnosed with this condition (5). The patient we present is the first described case in Slovakia. The disorder usually afflicts younger, otherwise healthy individuals.
In 2004, Walker presented characteristic bimodal distribution with one peak in childhood age and the second in the third decade of life (5). The youngest patient in whom frosted branch angiitis syndrome has been diagnosed was 2 years old (8), and the oldest 42 (10). There is a marked predominance of women (61%) in the number of cases as opposed to men (39%). Our patient was a man aged 20 years, and with the exception of the fact that he had overcome influenza approximately one month before the first symptoms of deterioration of vision, he had not been treated for any condition.
The most frequently occurring symptom of frosted branch angiitis syndrome is subacute loss of vision. Visual acuity may be substantially reduced, even to mere light perception. Almost 75% of patients in the described cases were afflicted bilaterally. Typical frosted branch angiitis syndrome has a conspicuous basic image, bilateral retinal vasculitis with perivascular exudates, with an image of frozen branches. The branches of the retinal blood vessels are coated from the disc of the optic nerve to the periphery, with veins affected more frequently than arteries. Intraretinal haemorrhages are sometimes also present, with mild to medium uveitis and vitritis. According to the scope of the pathology, infiltration of the macula and edema of the disc of the optic nerve may be present. On the basis of the data from the literature, we believe that our patient met the criteria for frosted branch angiitis syndrome.
Upon examination by fluorescence angiography (FAG), symptoms of later infiltration from the blood vessels are usually present, but without reduced flow of blood or symptoms of vascular occlusion. In the acute phase of the disorder we did not implement FAG examination for technical reasons.
The majority of authors (1, 3, 5, 8, 10, 11, 12) state a very good therapeutic effect of generally administered corticosteroids. However, on the basis of their experiences, Kadoya et al. (6), Isobe et al. (7), Browning et al. (9), Yoshida et al. (13), Narita et al. (14), Vander et al. (15) and others have expressed doubts with regard to the significance of corticosteroids in the case of this disorder. Browning (9) described a unilateral mild form of frosted branch periphlebitis in a healthy, 28 year old woman. Regression of papillitis and vasculitis occurred following a subconjunctival injection of 30 mg Triamcinolone. Vander et al. (15) describe a regression of vasculitis only following local therapy by corticosteroids. In our patient we recorded a rapid improvement of visual functions and the objective finding before the commencement of corticotherapy. The patient used antiphlogistics and antibiotics generally. Positive antibodies of class IgA and IgG against Chlamydia trachomatis were determined. Rovamycin recommended by the district ophthalmologist may have been effective. Following the completion of the course of Rovamycine, the patient was re-treated with Deoxymykoin upon the recommendation of the infectologist.
An image of vasculitis with a clinical picture of frozen branches of retinal blood vessels has also been described in patients with a general disorder. Ridley et al. (16) determined a diagnosis of large-cell intraocular lymphoma on the basis of an examination of a sample of the vitreous body in 1992. Kim et al. (17) described a unilateral image of this syndrome in an 18 year old patient with acute lymphoblastic leukaemia. Quillen et al. (18) described this syndrome in a 37 year old man with Crohn's disease, as did Jokhura et al. (19) in a female patient with aseptic meningitis. Generally administered corticoids had a favourable influence on the ocular and neurological symptoms.
Further studies point to a possible connection between retinal vasculitis and an infectious etiology. Greek authors (20) demonstrated HSV2 in a 30 years old man with vasculitis with frozen branches in the anterior chamber fluid using the PCR method.
Recurrence of the pathology has not yet been described.
We do not have any information from our patient, who is currently working abroad, concerning general or ocular complaints. According to the available data, the prognosis is not always favourable. Kleiner et al. (4) describe the formation of discifform scars in a patient with frosted retina periphlebitis. They also described later complications, neovascularisations as a consequence of vein occlusion and in one patient they recorded a retinal crack, with ablation of the posterior vitreous membrane with adhesion to the retina. Ito et al. (1) describe atrophy of the DON.
From the works published to date, it is evident that a clinical picture of retinal vasculitis with frozen branches may be caused by various diseases. Kleiner noted this fact in 1997 (3). On the basis of the data from the literature, we believe that in our patient this concerned a case of secondary vasculitis with frozen branches, with positive serology for Chlamydia trachomatis.

## CONCLUSION

The precise cause of frozen branch angiitis syndrome is unknown. The typical inception following a multifactorial prodromal pathology leads to the presupposition that this concerns a hypersensitive reaction to various infectious

agents, which may trigger the origin of frozen branch angiitis syndrome via the formation of immune complexes. In patients with a severe disruption of central visual acuity, this fact supports an indication for systemic corticotherapy. Because the results of central visual acuity in patients with or without systemic corticotherapy are not clear, to date no criteria have been set for treatment by corticoids in a patient with frozen branch angiitis syndrome. It is necessary to consider frozen branch angiitis syndrome to be a clinical ocular syndrome or a clinical symptom of a general pathology. It is necessary to approach patients with this pathology individual and to investigate the possible cause. Until the determination of the etiology, it is necessary to consider the method of treatment on the basis of the seriousness of the deterioration in central visual acuity and also of the clinical picture.

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