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DOCTORAL THESIS

THERAPEUTIC OPTIONS IN PATIENTS DIAGNOSED WITH NONINFECTIOUS INTERMEDIATE UVEITIS

A B S T R A C T

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1. GENERAL PART

1.1. THEORETICAL NOTIONS AND EPIDEMIOLOGY

Uveitis refers to a group of inflammatory disorders that cause inflammation and damages the structures of the eye. Uveitis affects the visual acuity from slightly reduced vision up to blindness. The term “uveitis” is used because the diseases usually involve a part of the eye called the uvea. Uveitis defines an inflammation of the uvea which is the vascular layer of the eye. However, uveitis is not centred on the uvea. These disorders may also affect the lens structure, vitreous, retina and the optic nerve leading to reduced vision or blindness. Uveitis may be caused by inflammatory processes occurring in the eye or it can be part of a general inflammatory disease affecting other organs of the body . It may appear at any ages and principally affects young and middle age population (20-60 years). Depending on the period of activity, uveitis can be acute or chronic (5). Some types of uveitis may recur, and episodes of active uveitis may be described.

The prevalence of uveitis is 38–714 cases per 100,000. It causes 10% up to 15% of blindness cases in the modern world. Younger people are mostly affected, and the indirect financial costs represent a higher general concern in the medical system. Approximately 5% of the uveitis cases are reported among children. There is no cause detected for anterior uveitis in 50% of the paediatric cases. Approximately 50% of paediatric uveitis cases are posterior, most commonly due to toxoplasmosis. About 25% of paediatric uveitis is intermediate.

1.2. ANATOMY

The visual function is performed by the eyeball and it generates about 90% of the external information. The anatomical features of the eyeball are spherical shape, anteroposterior diameter approximately 25-26 mm, transverse diameter 24.5 mm, vertical diameter 23.7 mm, anteroposterior axis of the eye is about 24 mm, the mass of the eyeball varies between 7 and 7.5 g.

The eyeball is sheltered by orbits. The eyeball is made up of three overlapping layers that make up its walls and transparent media.

Inside the eyeball there is the aqueous humour, the lens and the vitreous body, which represent the transparent media and together with the cornea, make up the optical system of the eye. In addition to these structures, the adnexa of the eyeball are eyelids, eyebrows, eyelashes, the tear apparatus, extraocular muscles.

1.3. DEFINITION, CAUSES, AND SYMPTOMS

Uveitis represents an inflammatory reaction that occurs into the eye. The body’s way to respond to different attacks like infection, tissue destruction and toxin is to create an inflammatory reaction. The pathophysiology mechanism of the inflammation is described as a migration of leukocytes into the damaged area to control or eliminate the insult. As a result, swelling in macular area(MO), redness and heat appear.

Causes of uveitis: autoimmune attack, intraocular or general infections or tumours, lesions of the eye, toxins in the content of the eye.

In a lot of cases the cause is undetermined.

Uveitis associated diseases: acquired immune deficiency syndrome, Behcet’s syndrome, herpes zoster infection, ankylosing spondylitis, cytomegalovirus retinitis, histoplasmosis, rheumatoid arthritis, multiple sclerosis, reactive arthritis, psoriasis, Kawasaki disease, toxoplasmosis, tuberculosis, syphilis, ulcerative colitis, sarcoidosis, Vogt Koyanagi Harada’s disease.

Symptoms of uveitis

Uveitis can be monocular or binocular. The onset of symptoms may be fast and is characterised by blurry, foggy vision, dark, floaters, eye pain, redness of the eye, photophobia, decreased vision.

Depending on the type of inflammation the signs and symptoms of uveitis may vary.

Acute anterior uveitis describes the inflammatory reaction that affects the anterior pole. It can affect one eye or even binocular in more severe cases. In adults, this type of uveitis is characterized by: pain, blurry vision, photophobia, a small pupil, redness.

Intermediate uveitis: foggy vision, decreased visual acuity, floaters, pain is not a common symptom.

Posterior uveitis may lead to blindness. In order to diagnose this type of inflammation, a complex ocular exam must be performed.

1.4. CLASSIFICATION

Anatomically uveitis may be classified as anterior, intermediate, posterior, or pan uveitis. Anterior uveitis typically characterises the inflammation of the anterior chamber and iris. Intermediate uveitis defines the inflammatory reaction of the ciliary body and vitreous humour. Posterior uveitis defines the inflammatory reaction of the retina, choroid, or the optic disc. Pan uveitis describes the inflammation of the whole uveal tract. There are different types of uveitis depending on the ocular region which is affected, if the inflammation involves one or both eyes, if onset is fast or progressively , if the inflammation can be controlled or stopped with treatment (acute or recurrent acute), or if it reappears (chronic). The most common presentation for uveitis is acute anterior uveitis (AAU). Anterior uveitis refers to the front portion of the uvea, the iris and ciliary body, which are primarily affected by the inflammation. Inflammatory cells in anterior uveitis may be present in the anterior chamber, and sometimes in the anterior vitreous. Acute form is characterized by a sudden onset and limited duration. The episode may be unique, or may be recurrent, with symptoms and signs reappearing after at least three months of absence of inflammation and no therapy. In contrast to chronic disease, where inflammation recurs once the medication is tapered and stopped. Intermediate uveitis is defined as a chronic, recurring entity which has a subtle onset. According to the Standardization of Uveitis Nomenclature (SUN) working group criteria, IU is defined as an intraocular inflammation mainly affecting the vitreous and peripheral retina. Posterior uveitis refers to an inflammation that primarily affects the retina and/or the choroid. The retinal and choroid changes include focal retinitis and choroiditis, multifocal retinitis and choroiditis. Optic disc and peripapillary involvement may be seen in the setting of posterior uveitis.

Pan uveitis refers to inflammation of all the structures of the uvea, which include the iris, ciliary body, and choroid. The inflammation can also affect the lens, the vitreous, the retina, the optic nerve and causes reduced vision or even blindness.

Depending on the infectious aetiology the disease it can be described as infectious or non-infectious uveitis. Uveitis is also classified as granulomatous and non-granulomatous. Granulomatous uveitis is characterized by mild pain, excessive tearing, blurry vision and mild sensitivity to light. Non-granulomatous uveitis is characterized by acute onset, pain, and photophobia. The acute form of non-granulomatous uveitis is associated with certain viral infections: herpes simplex and herpes zoster, Lyme disease, trauma, autoimmune diseases linked to HLA B27 (psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease, psoriatic arthritis), idiopathic arthritis, Fuchs heterochromic iridocyclitis, syphilis, tuberculosis, or sarcoidosis.

2. TREATMENT

Treatment of uveitis is still considered a challenge, regardless of many existing treatment options: corticosteroids, nonsteroidal anti-inflammatory drugs, immunosuppressive agents, and biological agents. Various drug delivery routes can be used for administration, each path having its own merits and demerits.

2.1. CORTICOSTEROIDS

Systemic or local corticosteroids remain the first-line therapy for the control of the inflammation in uveitis. Corticosteroids have an important role in treating macular oedema because of their high anti-inflammatory properties by preventing leukocyte migration, stabilizing endothelial cell tight junctions and also inhibiting synthesis of vascular endothelial growth factor (VEGF), prostaglandins, and proinflammatory cytokines. Intravitreal administration helps to prevent adverse effects generated by their systemic administration.

2.2. INTRAVITREAL TRIAMCINOLONE ACETONIDE INJECTION

Triamcinolone acetonide (TA) is the most common used corticosteroid for the treatment of uveitic central macular oedema (CMO). Injected intravitreally, TA has a mean half-life of 18.6 days in non-vitrectomized eyes and 3.2 days in vitrectomized eyes. A unique dose of 4 mg injected as a suspension in vitreous cavity of a non-vitrectomized human eye is known to maintain a beneficial drug concentration for approximately 3 months due to its decreased water solubility. It has been appreciated that a single intravitreal injection of TA can reach a concentration of 0.22 ± 0.24 μg/ml.

2.3. INTRAVITREAL DEXAMETHASONE

In comparison with TA dexamethasone (DEX) which is a water-soluble, synthetic glucocorticoid is three times more efficient. Because of the fact that it is a small molecule, it is rapidly removed from the vitreous, with an estimated vitreal half-life of 5.5h.

2.4. PARS PLANA VITRECTOMY

In case of refractory macular oedema and persistent vitreous haze not responding to drug therapy, posterior vitrectomy can be considered as a last resort.

3. ACTUALITIES

3.1. OUTCOME OF INTRAVITREAL TRIAMCINOLONE IN UVEITIS

The following study was conducted by: Kok H, Lau C, Maycock N, McCluskey P, Lightman S.

The purpose of the study was to evaluate the short-term outcome of intravitreal triamcinolone acetate (TA) in the treatment of uveitic cystoid macular oedema (CMO).

Results: The mean follow-up was 8.0 months (range, 3-51), and the mean improvement of VA after intravitreal TA was 0.26 (from 0.65 to 0.39 logarithm of the minimum angle of resolution: Snellen, 6/24-6/12, approximately).

In conclusion, in patients with uveitic CMO, intravitreal TA can reduce CMO and improve VA and, in some cases, allows the tapering and/or reduction of immunosuppressive therapy.

3.2. LONG-TERM OUTCOME OF INTRAVITREAL TRIAMCINOLONE ACETONIDE INJECTION FOR THE TREATMENT OF UVEITIS ATTACKS IN BEHÇET DISEASE

This study was conducted by: Park UC, Park JH, Yu HG.

The purpose of this study was to evaluate the long-term efficacy and safety of intravitreal triamcinolone acetonide (IVTA) injection for posterior segment inflammation in Behçet disease patients. Forty-nine (49) eyes were included in the study. The follow-up period was 24 months.

The study results revealed that the mean BCVA improved from 0.89 logMAR units to 0.70, 0.64 at 12, 24 months, respectively. In 87% of patients the vitreous haze has completed resolved after 6 months, but 60% of them experienced relapse within 12 months. 30.6% had more than one injection in 24 months, 80% one repeat, 20% 2 repeats, that did not influence the BCVA. The study concluded that in this cases IVTA injection is an effective therapeutic option, even if ocular complications could limit its potential.

EXPERIMENTAL PART

1. STUDY DESIGN

1.1. PURPOSE OF THE STUDY

To determine the effectiveness of intravitreal Triamcinolone Acetonide in reducing vitreous haze (VH), central macular oedema (CMO) and improvement of the visual acuity, 3 months after treatment.

1.2. OBJECTIVES

For this study we completed four research lines:

A. Baseline evaluation of the patients

Medical history of inflammatory/autoimmune diseases, infectious background. Some of the patients included in the study had already been diagnosed with an autoimmune disease, but the majority had no positive diagnosis of any disease. Four patients had a positive diagnosis of Behçet disease, 3 had sarcoisosis, and 1 had juvenile arthritis.

In order to establish the ocular diagnosis, we performed a series of general and ophthalmological investigations.

B. Perform one intraocular injection with TA in all patients

Triamcinolone acetonide is a synthetic corticosteroid that can be used topically, intra-articular and intraocular. Intravitreal Triamcinolone acetonide has been used to treat various eye diseases and has been found useful in reducing macular oedema.

C. Administrating oral cortisone 1 mg/kg body weight to patients with BCVA < 0.7 df (> 0.2 LogMAR)

Even though many cases of intermediate uveitis are not at the moment of diagnosis associated with other general diseases, scientists have proven that combining intraocular cortisone with general (oral) administration may help in reducing the intraocular inflammation.

D. Perform a 3 months follow-up for the following parameters: BCVA, vitreous haze (VH), macular oedema (MO), presence of ocular or general symptoms, ocular and general side effects (IOP, degree of inflammation, general well-being).

1.3. INCLUSION CRITERIA

1. Positive diagnosis of intermediate non-infectious uveitis.
2. IOP ≤ 20 mmHg.
3. Signed informed consent.

1.4. EXCLUSION CRITERIA

1. Age ≤18 years.
2. Ocular or general infections in the last 6 months.
3. History of ocular Toxoplasma or Toxocara.
4. Ocular surgery in the last 3 months.

1.5. PRIMARY OBJECTIVES

- Assess the change in BCVA (Best Corrected Visual Acuity) 3 months after the intervention.
- Assess the evolution of the VH (Vitreous Haze) class, 3 months after the intraocular injection.
- Evaluate the success rate in the presence of the Macular Oedema 3 months after the treatments.

1.6. SECONDARY OBJECTIVES

- Assess the presence of the ocular and general symptoms 3 months after the intraocular injection.
- Assess the presence of the ocular and general side effects 3 months after the intraocular injection.
- Evaluate the change in IOP (Intraocular pressure) 3 months after the treatment.

1.7. MATERIAL AND METHODS

The present study is a retrospective, interventional, comparative assessment with consecutive enrolment of patients affected by non-infectious intermediate uveitis.

All subjects expressed in writing, prior to enrolment, their informed consent to be subjected to appropriate intermediate uveitis reduction techniques.

The study was conducted between 2018-2020.

The study received the Local Ethics Committee of the Clinic “Centrul Oftalmologic Prof. Dr. Munteanu” approval and was conducted in accordance with the Declaration of Helsinki and with the “International Standard of Good Clinical Practice (ICH-GCP E6 Step 4)”.

1.7.1. Method

Each patient received a single intravitreal injection of 4 mg triamcinolone acetonide. Local antibiotic drops were spread on and drops of oxybuprocaine 0.4% were administered. All injections were performed in the operating room. After topical disinfection with povidone-iodine, the sterile field and the lid speculum were applied. After 30 seconds another drops of 0.4% oxybuprocaine were administered. Injections were performed using 30-gauge needles through the inferotemporal pars plana, 4 mm from the limbus. After the injection, local antibiotic drops were instilled. A protective eye bandage was applied for a few hours after the procedure.

Depending on the clinical condition of the 50 patients, they were assigned to one arm of the study. The criteria for applying the general treatment was a BCVA below 0.7 df. Thirty-eight (38) patients fell under the above-mentioned criteria. Eleven (11) patients refused the general (oral) treatment so they were given only the IVTA treatment. Consequently, 27 patients received, in addition to the IVTA treatment, the general treatment. Twenty-three (23) patients received only the IVTA treatment.

Oral cortisone scheme. 27 patients with BCVA < 0.7 df (> 0.2 LogMAR) received oral cortisone treatment by following the scheme: 1 mg/kg body weight for 7 days, tapered weekly, up to ¼ pill during the last week of treatment. The patients were followed for 3 months after the treatment. The following were recorded at the baseline (preoperative) and after 3 months from the intervention (postoperative):BCVA, symptoms, macular oedema presence, vitreous haze

class, central macular thickness, intraocular pressure. In addition, postoperative treatment side effects were recorded (if the case).

Macular oedema was defined as thickening of the retina (centre point thickness ≥ 260 μm) on time-domain optical coherence tomography (OCT) of macula (134). The target for our study was ≥ 20% reduction in central point thickness on OCT.

To evaluate the vitreous haze, the Grading Scheme for Vitreous Haze was used.

The age and sex of the subjects enrolled for the purpose of demographic analysis and the stratification of the results into different interest groups were also collected at baseline (preoperative).

Study Groups

We divided the cohort of 50 patients into the following groups:

• Group 1: 23 patients with IO(IVTA) treatment only.

• Group 2: 27 patients with IO (IVTA) treatment and General (oral) treatment.

1.7.2. Statistical analysis methods

The statistical analyses and the graphics were done with the help of R version 4.0.0 (135) and MedCalc™ version 19.2.0.

2. RESULTS

The obtained results were divided into two categories: primary and secondary, causally related to the proposed objectives.

Our study took place between 2018-2020 and was structured in such a way that the patient is monitored frequently.

2.1. DEMOGRAPHICS

2.1.1. Demographics for all study participants

The study is balanced in terms of the number of males and females (chi-square test; $p = 0.40$), even if there are differences in favour of the former.

No statistically significant differences were observed between males and females in the age of the 50 subjects enrolled in the study (Wilcoxon-Mann-Whitney test; $p = 0.50$).

2.2. RESULTS FOR PRIMARY OBJECTIVES

2.2.1. Best corrected visual acuity (BCVA)

To evaluate the change in BCVA (LogMAR) from baseline to 3 months follow-up we performed Wilcoxon signed-rank tests for all patients and by treatment group. Results proved highly significant for all patients (Wilcoxon signed-rank test, $p < 0.001$). In the case of patients subjected to IVTA + General treatments, the results showed also high statistically significance (Wilcoxon signed-rank test, $p < 0.001$). Statistical significance was achieved also in the case of patients subjected only to the IVTA treatment, although it was only marginal (Wilcoxon signed-rank test, $p = 0.03$).

2.2.2. Assess the evolution of the vh (vitreous haze) class 3 months after the intraocular injection

To determine if the treatments influence the Vitreous Haze phenomenon, we recoded the Vitreous Haze Grading Score as a binary (2 levels only) variable. All values with a scoring grade less or equal to 1 were labelled as low, the rest (grades from 2 to 5) as high.

Both treatment variants have a positive impact in the sense of reduction of the vitreous haze phenomenon.

We determined that the best treatment is the combined solution (IVTA + General), with an average 88.9% success rate (McNemar's test, $p < 0.001$). The second variant is also (marginally) effective in reducing VH, with an average 30.4% success rate (McNemar's test, $p = 0.016$). The difference in treatments' success rate is statistically significant in the favour of the combined treatment (proportions test, $p < 0.001$, diff. 58.5%, 95%CI: 32% - 75%).

2.2.3. Evaluate the success rate in the presence of macular oedema 3 months after the treatments

Macular Oedema presence was established at baseline and 3 months follow-up examination. Success was established when a patient with Macular Oedema at baseline recorded a reduction of more or equal to 20% in CMT (Central Macular Thickness) at 3 months follow-up. The success rate was obtained by dividing the number of successes by the total number of patients with MO at baseline.

Both treatments were effective in reducing the Central Macular Thickness. The IVTA only treatment had a success rate of 60.0% and the reduction in CMT from baseline to 3 months follow-up was 24.2% (statistically significant, $p = 0.002$). The IVTA + General treatment had a success rate of 72.0% and the reduction in CMT from baseline to 3 months follow-up was 33.1% (statistically significant, $p < 0.001$).

There were not any statistically significant differences between treatments in success rates ($p = 0.09$) and CMT reductions ($p = 0.70$).

2.3. RESULTS FOR SECONDARY OBJECTIVES

2.3.1. Assess the presence of the ocular and general symptoms 3 months after the intraocular injection

Before treatment 42 patients accused ocular symptoms specific to intermediate uveitis: blurred, foggy, decreased visual acuity and floaters. 3 months after treatment, 22 patients still accused ocular symptoms, but less intense. On one side, symptoms reduced after intraocular and/or general treatment, on the other side, more intraocular injections and/or general treatment need to be administered to reach a full recovery, if possible.

15 patients had subconjunctival haemorrhage after the intraocular injection and reported a scratchy feeling on the surface of the eye, which disappeared after 2 weeks.

2.3.2. Assessment of the presence of ocular and general side effects 3 months after the intraocular injection

Most of the side effects of the intra-ocular treatment are seen soon after the injections are made.

In our study one side effect was subconjunctival haemorrhage in 15 patients, that disappeared after 2 weeks. The only treatment administered was artificial tear eye drops for 2 weeks. The subconjunctival haemorrhage did not cause any change in the visual acuity, no discharge from the eye and no pain. Subconjunctival haemorrhage is a minor side effect, that does not cause early or long-term complications and is related to the needle puncture of the conjunctiva vessels.

Another side effect induced by the injection content, triamcinolone acetonide, was raised intraocular pressure, defined as IOP ≥ 20 mmHg. In our study 6 patients presented high intraocular pressure, the first day after the injection procedure, for which they received local treatment with dorzolamide / timolol 20 mg/ml+5 mg/ml for 1 month.

An important side effect was sterile endophthalmitis which occurred in 3 cases. All patients received local treatment with topical antibiotics, prednisolone acetate and cycloplegic eye drops; the vitreous inflammation resolved within 3 weeks in the first case and within 4 weeks in the other two cases. Our conclusion that these were cases of sterile, rather than

infectious endophthalmitis was based on the resolution of the inflammation without the use of intravitreal antibiotics.

2.3.3. Evaluation of the iop (intraocular pressure) fluctuations 3 months after the treatment

One of the criteria for including the patients in the current study was an intraocular pressure (IOP) at baseline visit (before treatment) of less or equal to 20 mmHg. After 3 months from the treatments 6 patients had a high IOP (> 20 mmHg), 2 from the IVTA only group and 4 from the combined treatment group.

Both treatments increased IOP at 3 months follow-up visit. The increase of 12% from the baseline to final visit was only marginally statistically significant in the case of IVTA only treatment (Wilcoxon signed-rank test, $p = 0.049$). For the IVTA + General combined treatment the increase by 22% from the baseline to the final visit was statistically significant (Wilcoxon signed-rank test, $p = 0.017$). Considering all patients, the increase by 16% in IOP was statistically significant (Wilcoxon signed-rank test, $p = 0.002$). However, the difference in percent of IOP increases between the 2 treatment groups were not statistically significant (proportions test, $p = 0.357$,95% CI: -12% - 30%).

In our study 6 patients presented high intraocular pressure, the first day after the injection procedure, for which they received local treatment with dorzolamide / timolol 20 mg/ml+5 mg/ml for 1 month. After one month of treatment, the intraocular pressure was normal, and the hypotensive treatment was stopped.

3. DISCUSSIONS

IV triamcinolone alone or combined with general cortisone administration has been shown to be successfully when used control intermediate noninfectious uveitis. The parameters monitored in our study are the following:

- BCVA, both treatment groups showed statistically significant improvements in visual acuity from baseline to 3 months follow-up;
- VH (VITREOUS HAZE) CLASS, both treatment variants have a positive impact in the sense of reduction of the vitreous haze phenomenon.
- SUCCESS RATE IN THE PRESENCE OF MACULAR OEDEMA, both treatments were effective in reducing the Central Macular Thickness
- ASSESS THE PRESENCE OF THE OCULAR AND GENERAL SYMPTOMS, 15 patients had subconjunctival haemorrhage after the intraocular injection and reported a scratchy feeling on the surface of the eye, which disappeared after 2 weeks.
- ASSESSMENT OF THE PRESENCE OF OCULAR AND GENERAL SIDE EFFECTS. In our study 6 patients presented high intraocular pressure. An important side effect was sterile endophthalmitis which occurred in 3 cases.
- EVALUATION OF THE IOP (INTRAOCULAR PRESSURE) FLUCTUATIONS.In our study 6 patients presented high intraocular pressure

Another reference study for the outcome of IV triamcinolone is the study named OUTCOME OF INTRAVITREAL TRIAMCINOLONE IN UVEITIS, conducted by: Kok H, Lau C, Maycock N, McCluskey P, Lightman S.

The purpose of the study was to evaluate the short-term outcome of intravitreal triamcinolone acetate (TA) in the treatment of uveitic cystoid macular oedema (CMO).

Results: The mean follow-up was 8.0 months (range, 3-51), and the mean improvement of VA after intravitreal TA was 0.26 (from 0.65 to 0.39 logarithm of the minimum angle of resolution: Snellen, 6/24-6/12, approximately).

In conclusion, in patients with uveitic CMO, intravitreal TA can reduce CMO and improve VA and, in some cases, allows the tapering and/or reduction of immunosuppressive therapy.

4. CONCLUSIONS

1. Demographic data. Regarding the age of the patients, our study confirms the statement that uveitis typically affects patients ages 20 to 60 years.

2. Best corrected visual acuity (BCVA). Globally, for all 50 patients, the mean ±SD visual acuity gain was 0.29 ±0.27 LogMAR.

3. Vitreous haze. In conclusion, both treatment variants have a positive impact in the sense of reduction of the vitreous haze phenomenon.

4. Macular oedema. In conclusion, both treatments were effective in reducing the Central Macular Thickness. The IVTA treatment group had a success rate of 60.0% and the IVTA + General treatment had a success rate of 72.0%.

5. Symptoms and side effects. An important side effect was sterile endophthalmitis which occurred in 3 cases. Our conclusion that these were cases of sterile, rather than infectious endophthalmitis was based on the resolution of the inflammation without the use of intravitreal antibiotics.

6. Intraocular pressure. After 3 months from the treatments 6 patients had a high IOP (> 20 mmHg), 2 from the IVTA only group and 4 from the combined treatment group.

7. Our study proves that both types of cortisone administration have a positive effect on intermediate non-infectious uveitis that lasts for at least 3 months period.

8. Intravitreal cortisone administration is an efficacious option to general cortisone administration as it can avoid systemic side effects but obtain a sufficient therapeutic quantity in the vitreous body.

9. General cortisone treatment is still an important tool in treating non-infectious uveitis, regardless of their connection with known or unknown systemic conditions. General cortisone also plays a significant role in the treatment of non-infectious uveitis that are limited to the eye.

10. According to the literature review and demonstrated by our study, the administration of IVTA increases the visual acuity and can control the level of ocular inflammation. The combination of IVTA and oral cortisone is more effective in patients with macular oedema and intense vitreous haze. It is agreed by most specialists, that in patients with bilateral uveitis, systemic medication is needed.

5. OWN CONTRIBUTIONS

1. After a complex literature review, we may report the fact that there is no other study performed on non-infectious uveitis in Romania, so our study is a pioneer in this field.

2. Regarding the scientific importance of the presented study, the number of eyes included in this study, is consistent enough to draw relevant conclusions about the effectiveness of general and intraocular treatment. The number of eyes included in this study is in line with the number of eyes reported in international studies on non-infectious uveitis.

3. The patients' distribution into two study arms is an original element, which allowed the researcher to propose treatment options for patients with non-infectious uveitis.

4. Taking into consideration the fact that the cost of oral and/or intravitreal cortisone is affordable, the proposed treatment options represent a real factor that may be implemented in large population mass, even in our country. The presented study originally highlights the cost/effectiveness ratio of oral and intravitreal cortisone.

5. The treatment approaches demonstrated in this study may be used by all ophthalmologists to better control the inflammatory reactions in non-infectious intermediate uveitis.

6. In Romania, the presented study represents a starting point in the research of non-infectious intermediate uveitis and can be continued with a larger number of treated eyes and a longer period of follow-up.