(16)

Latanoprost is effective in reducing high intraocular pressure associated with Graves' ophthalmopathy

Latanoprost jest skutecznym lekiem obniżającym ciśnienie wewnątrzgałkowe w jaskrze związanej z orbitopatią w przebiegu choroby Gravesa i Basedowa

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Abstract: Purpose: To assess the efficacy and tolerability of latanoprost in the treatment of glaucoma and ocular hypertension associated with Graves' ophthalmopathy. Prospective interventional case series.
Materials and Methods: 28 patients (19 females and 9 males) aged from 31 to 68 (mean age 45.5± 5.6), presenting with diagnosis of Graves' ophthalmopathy and intraocular pressure equalto 25.0 mmHg or more. 18 Patients presented with inflammatory stage of Graves' ophthalmopathy. 22 patients were within the first two years from the onset of symptoms of Graves' ophthalmopathy. 6 patients had exophthalmos and history of active Graves' ophthalmopathy. Intraocular pressurewas measured before treatment, and at two, four and six weeks of treatment with latanoprost at 9 am. Ocular symptoms and signs were noted before and after the treatment period.
Results: The mean baseline intraocular pressure was 26.6 ± 2.5 mmHg, ranging from 25.0 mmHg to 42 mmHg.
In two weeks of treatment, the mean intraocular pressure was 18.6 ± 2.3 mmHg (min 12.0 mmHg, max 27.0 mmHg). At 4 weeks mean intraocular pressure was 18.4 ± 2.2 mmHg (min 11.0 mmHg, max 28.0 mmHg). At 6 weeks mean intraocular pressure was 18.7 ± 1.9 mmHg (ranging from 11 mmHg to 25.0 mmHg). 3 patients experienced mild side effects.
Conclusions: Latanoprost is effective and well tolerated in the treatment of increased intraocular pressure associated with Graves' ophthalmopathy.

Key words: Graves' ophthalmopathy, Graves' disease, glaucoma, ocular hypertension, latanoprost.

Abstrakt: Cel: ocena skuteczności i bezpieczeństwa latanoprostu w leczeniu podwyższonego ciśnienia wewnątrzgałkowego oraz jaskry w przebiegu orbitopatii związanej z chorobą Gravesa-Basedowa. Prospektywne badanie interwencyjne.
Materiał i metody: w badaniu wzięło udział 28 pacjentów (19 kobiet i 9 mężczyzn) w wieku od 31do 68 lat (śr. 45,5± 5,6), z rozpoznaną orbitopatią w przebiegu choroby Gravesa-Basedowa oraz ciśnieniem wewnątrzgałkowym ≥ 25 mmHg. Objawy zapalne choroby miało 18 pacjentów. W przypadku 22 pacjentów upłynęło mniej niż dwa lata od wystąpienia pierwszych objawów orbitopatii. U 6 pacjentów obecny był wytrzeszcz oraz upłynęło więcej niż dwa lata od rozpoznania aktywnej fazy orbitopatii. Pomiaru ciśnień wewnątrzgałkowych dokonano przed rozpoczęciem leczenia, a następnie po dwóch, czterech i sześciu tygodniach od rozpoczęcia leczenia. Objawy oczne orbitopatii oceniono na początku i na końcu leczenia.
Wyniki: wyjściowe średnie ciśnienie wewnątrzgałkowe wynosiło 26,6 ± 2,5 mmHg (od 25,0 do 42,0 mmHg). Po dwóch tygodniach leczenia średnie wartości ciśnienia kształtowały się w granicach 18,6 ± 2,3 mmHg (od 12,0 mmHg do 28,0 mmHg). Po czterech tygodniach leczenia średnie ciśnienie wynosiło 18,4 ± 2,2 mmHg (od 11.0 mmHg do 28.0 mmHg). Po 6 tygodniach leczenia średnie wartości ciśnienia kształtowały się w granicach 18,7 ± 1,9 mmHg (od 11,0 mmHg do 25,0 mmHg). Objawów ubocznych latanoprostu doświadczyło 3 pacjentów z badanej grupy.
Wnioski: latanoprost jest skutecznym i bezpiecznym lekiem obniżającym ciśnienie wewnątrzgałkowe u chorych na jaskrę i nadciśnienie wewnątrzgałkowe, które mają związek z orbitopatią w przebiegu choroby Gravesa-Basedowa.

Słowa kluczowe: orbitopatia w przebiegu choroby Gravesa-Basedowa, jaskra, nadciśnienie wewnątrzgałkowe, latanoprost.

The increased intraocular pressure (IOP) is a well recognized symptom occurring in Graves' ophthalmopathy (GO) (1, 2). In the Guidelines of European Glaucoma Society, glaucoma associated with Graves' disease has been classified as secondary, with elevated episcleral venous pressure. Recommended first line treatment should address the underlying cause (3).

The evidence regarding the increased prevalence of glaucoma associated with thyroid disease is equivocal. Some studies

indicate increased prevalence (4, 5) and some claim the rates of glaucomatous optic nerve damage are similar to general population (6–8). The elevated episcleral venous pressure is thought to be the main reason for the increased IOP in active stage of Graves' ophthalmopathy (5).

Graves' ophthalmopathy is a chronic autoimmune inflammatory process involving lymphocytic infiltrate and accumulation of glycosaminoglycans within the orbital tissues. In the late stage fibrosis predominates (9). Treatment of active inflammatory stage is glucocorticosteroids or radiotherapy (10). Recommended treatment depends on the severity of inflammatory signs, presence of corneal complications, signs of the optic nerve compression (11) and also the extent to what the quality of life is compromised (3).

Not every patient with significantly elevated intraocular pressures is qualified for intravenous immunosupression with steroids or for radiotherapy. Also, very few patients undergo orbital decompression surgery.

Glucocrticosteroids may cause secondary glaucoma or may be contraindicated for other reasons (12). Orbital decompression surgery has only mild effect on IOP and is not indicated for mild cases of GO (13). Treatment of inactive stage of GO consists of cosmetic reconstructive surgery. Thus the question of anti-glaucoma medication usage in thyroid ophthalmopathy is valid and important.

In a proportion of patients with ophthalmopathy, the clinician is faced with significantly elevated intraocular pressure with or without central visual field scotomas, and the dilemma of choosing the best management.

Latanoprost is prostaglandin F2α analogue, with proven IOP lowering effect (14). Its main mechanism of action is to increase in uveoscleral out flow (15). It is a very common first line choice for primary open angle glaucoma (POAG) and ocular hypertension (OH). It is not known, what the intraocular pressure lowering effect of latanoprost is in patients with GO.

We conducted a study to assess the efficacy and tolerance of latanoprost in the patients with high intraocular pressures and concomitant active and inactive Graves' ophthalmopathy.

Material and methods

33 patients presented to the Department of Ophthalmology with GO and intraocular pressure above 25.0 mmHg, between May 2011 and June 2013.

We included 28 patients, over 18 years of age,19 female and 9 male remaining under joint care of the department of Endocrinology and Ophthalmology of the Medical University of Lodz, with GO and intraocular pressure over 25.0 mmHg, who have not met exclusion criteria.

4 patients were excluded because of pseudoexfoliation syndrome, and 1 because of pre-existing open angle glaucoma.

18 patients had inflammatory symptoms of GO. 22 patients were within the first two years from the onset of symptoms of GO. 6 patients have been were more than two years from the onset of orbitopathy symptoms, had exophthalmos and inactive GO.

In order to enroll the patient in the study at least two independent measurements above 25.0 mmHg, in the same eye, had to be obtained, at least three days apart, corrected for central corneal thickness (CCT). From 18 patients in the study, with inflammatory GO, 12 were not planned for immunomodulatory treatment and 6 have completed at least 1 month of immunomodulatory treatment. 3 of these patients have IOP above 25.0 mmHg before the treatment with steroids and the treatment failed to reduce the pressure below 25.0 mmHg. Subsequent 3 patients developed IOP above 25.0 mmHg while on steroid treatment.

The study protocol was approved by the Ethics Committee of the Medical University of Lodz and conducted according to the tenants of Helsinki Declaration. All patients gave their full informed consent.

Exclusion criteria

The exclusion criteria were: pregnancy and lactation, glaucoma on treatment before the onset of Graves'disease, pseudoexfoliation, narrow or closed angle on gonioscopy, history of uveitis, neovascularization, history of intraocular surgery other than uncomplicated phacoemulsification, history of trauma, and allergy to latanoprost or benzalkonium chloride. We did not include patients in whom immunomodulatory treatment was planned or started within one month other. Reasons for exclusion were: severe cardiac or respiratory insufficiency or liver failure. Corneal exposure or epithelial defects were not considered the reason for exclusion.

Evaluation

All patients enrolled in the study had the confirmed diagnosis of Graves' disease. The TSH, T3, T4 and ABR-THS were assessed. Graves' orbitopathy was diagnosed in each patient clinically and radiologically. Time from the onset of the symptoms of Graves' disease and Graves' orbitopathy was noted. Current thyroid status was noted. Photographs were obtained for the purpose of comparing signs of orbitopathy at subsequent visits.

Full ophthalmic evaluation was performed with assessment of orbitopathy. Visual acuity was checked. Red saturation test was performed. Pupillary reactions including relative afferent pupilary defect were examined. Slit lamp examination was performed. Fundoscopy was performed following mydriasis with the slit lamp and +90 dioptrie lens. The IOP was measured with Goldmann applanation tonometry in the primary position, with the patient in the sitting position. The CCT was measured and IOP value was adjusted for the CCT. Gonioscopy was performed. Exophthalmos was measured with Hertel Exophthalmometer. Ocular motility was assessed. Restrictions were noted in four directions, in a four point scale. Inflammatory signs were noted if present, and the Clinical Activity Score was assessed (9). The cornea was assessed for epithelial integrity and the tear film was evaluated. The optic nerve head was assessed for oedema, cupping and other abnormalities. The macula and peripheral retina were inspected. Full threshold central visual perimetry was performed.

The IOP was measured twice. Both readings were at 9 am at least three days apart. The mean values of two measurements were taken into account. If the value was equal or above 25 mmHg, in one or both eyes, the patient was regarded as eligible for enrolment, provided no exclusion criteria were met. If IOP above 25 mmHg was noted in one eye only, this eye was enrolled in the study. If pressure above 25 mmHg

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was symmetrically elevated in both eyes, the study eye was chosen at random. If the pressure in both eyes was elevated above 25.0 mmHg, but the difference between the eyes was at east 1.0 mmHg, the eye with higher pressure was included in the analysis.

Treatment period

The patients were prescribed commercially available latanoprost (Xalatan, Pfizer Europe) and instructed to instil one drop in each eye at 8 pm everyday.

The intraocular pressure was measured on day 14, 28 and 42 (at 2 weeks, 4 weeks and 6 weeks) after treatment commencement. All measurements were performed at 9 am. The mean value of the three readings was taken into account. Ophthalmic evaluation was performed at each follow-up visit. Symptoms and signs of orbitopathy were evaluated at 6 weeks visit, and compared with the baseline status. Side effects were noted.

Results

The characteristics of the patients in the study are summarized in table I.

	Before treatment/ Przed leczeniem (n=28)	After 6 weeks of treatment with latanoprost/ 6 tygodni po leczeniu latanoprostem (n=28)
Eye irritation/ Podrażnienie oka	3	4
Blurred vision/ Zaburzenia widzenia	4	3
Conjunctival redness/ Zaczerwienienie spojówek	16	17
Conjunctival oedema/ Obrzęk spojówek	8	7
Tearing/ Łzawienie	14	8
Photophobia/ Światłowstręt	12	12
Itching/ Swędzenie	7	6
Eyelid oedema/ Obrzęk powiek	9	7
Dry eye/ Suche oko	1	2
Punctate epithelial defects/ Ubytki nabłonka rogówki	0	1
Headache/ Bóle głowy	1	0
Palpitations/ Kołatanie serca	1	1
Fatigue/ Zmęczenie	0	1
Dizzines/ Zawroty głowy	0	1

Tab. I. Ocular signs and symptoms in the study group before and after treatment.
Tab. I. Objawy oczne u pacjentów z badanej grupy – przed leczeniem i po jego zakończeniu.

3 patients had visual field defects consistent with neuroretinal rim abnormality, which was diagnosed as glaucoma. Further 5 patients had small visual field scotoma, which were considered related to orbitopathy or insignificant.

All patients have completed 6 weeks of treatment with latanoprost.

The mean baseline IOP was 26.6 ± 2.5 mmHg, ranging from 25.0 mmHg to 42.0 mmHg.

6 patients (2 female and 4 male) in the study had IOP over 25.0 mmHg in one eye only. Other patients had IOP over 25.0 in both eyes. All patients with asymmetrical intraocular pressure over 3.0 mmHg had also asymmetrical orbitopathy, with either asymmetrical exophthalmos or asymmetrical Clinical Activity Score. 18 patients in the study had the IOP of 25.0 or 26.0 mmHg. 7 patients had the IOP between 27.0 and 30.0 mmHg. 3 patients had the IOP ≥ 31.0 mmHg. Out of these three patients with severely elevated pressures two were in the active stage of orbitopathy with signs and symptoms of an active inflammation. One had associated choroidal folds. One was in an inactive stage of orbitopathy.

The mean IOP at two weeks was 18.6 ± 2.3 mmHg, ranging from 12.0 to 27.0 mmHg.

The mean IOP at four weeks was18.4 ± 2.2 mmHg, ranging from 11.0 to 28.0 mmHg.

The mean IOP at six weeks was18.7 ± 1.9 ranging from 11.0 to 25.0 mmHg.

There were no significant changes in the characteristics of orbitopathy between the baseline and the end of the treatment (Table II). None of the patients lost more than 1 line of visual acuity.

	Before treatment/ Przed leczeniem	After 6 weeks of treatment/ 6 tygodni po leczeniu latanoprostem
AbrTSH	16.4 ± 5.6	17.6 ± 6.1 (p = 0.00)
CAS	1.5 ± 0.8	
Exophthalmos (in the study eye)/ Wytrzeszcz oka badanego	21.6 ± 1.2	21.5 ± 1.0 (p = 0.00)
Restrictive myopathy (in the study eye)/ Myopatia restrykcyjna badanego oka	11 patients	11 patients (p = 0.00)
Dysthyroid optic neuropathy/ Neuropatia	1 patients	0
Choroidal folds/ Fałdy naczyniówki	2 patients	2 patients (p = 0.00)
Palpebral fissure width/ Szerokość szpary powiekowej	12.9 mm	13.0 mm (p = 0.00)

Tab. II. Characteristics of orbitopathy before and after treatment.
Tab. II. Charakterystyka orbitopatii przed leczeniem i po leczeniu.

Exophthalmometry readings did not change in any patient by more than 1.0mm. Also there were no changes in the pattern of extraocular muscle restrictions in any of the patients, in whom they were present. Inflammatory symptoms, such as

redness and oedema of the eyelids and conjunctiva have decreased slightly in 4 of 6 patients treated with immunosuppression in the course of the study. In one patient who was diagnosed with optic neuropathy visual acuity improved from 0.3 at baseline to 0.8 at the end of the study. One patient had choroidal folds, and one had discrete choroidal folds at baseline. The sign was still present at the end of the treatment period.

Discussion

Our study has demonstrated the efficacy of latanoprost in the treatment of elevated intraocular pressures and glaucoma in patients with Graves' ophthalmopathy. The intraocular pressure lowering effect of latanoprost was demonstrated at 2 weeks and maintained at 4 and 6 weeks. The treatment was generally well tolerated. We aimed to select for the study those patients in whom topical intraocular pressure lowering therapy was clinically indicated, and in whom we would not expect intraocular pressure reduction as a result of orbitopathy--specific therapies. Our treatment group consisted of all Graves' orbitopathy patients, who presented with intraocular pressure 25.0 mmHg or higher with active and inactive stage of the disease (9). We enrolled patients in whom steroid therapy was not indicated and not planned. Also, we included some patients on steroid therapy, but only those, in whom no reduction of IOP was observed following one month of treatment. The intraocular pressure increased following steroid treatment for inflammatory signs of Graves' ophthalmopathy in a few patients in our study group, the use of IOP lowering medication was considered mandatory in these cases.

It is not known whether intraocular pressure associated with orbitopathy should be treated more aggressively than primary ocular hypertension or maybe higher IOP is tolerable.

We assumed that patients with intraocular pressure of 25.0 mmHg, which persisted despite the pulse steroid therapy, should be prescribed intraocular pressure lowering medication. We assumed, for the purpose of the study, that 25.0 mmHg should be managed with IOP lowering medication.

Furthermore, we assessed symptoms and signs of orbitopathy, at baseline and at the end of treatment (16). The intraocular pressure is expected to decrease with the gradual resolution of inflammatory symptoms and signs of GO. Photographic documentation is the best way of documenting redness and oedema, in the standardized lighting conditions (16).

The minority of patients observed some mild improvement. This was also why we decided that 6 weeks, which is rather short period for observing the effect of latanoprost, would be the appropriate follow-up period for this study.

Latanopost is the first line treatment for primary open angle glaucoma and ocular hypertension (17, 18). It was not known whether it was safe and effective in patients with concomitant inflammatory and fibrotic Graves' orbitopathy. In our study patients with active and inactive stages of orbitopathy were included. In both groups the response to treatment with latanoprost was satisfactory. All patients experienced reduction of intraocular pressure.

It is a big challenge to assess side effects of latanoptost with co-existent orbitopathy, since many reported side effects, are identical with the symptoms of orbitopathy.

We have noted the pre-existent ocular signs and symptoms. They were very numerous and showed significant diversity. We noted all new symptoms and deterioration of pre--existent symptoms. Additionally, in relation to some symptoms we noted improvement during the course of the study. At final visit we compared the signs with the ones recorded at the first visit. We did not observe any general deterioration, and none of the patients discontinued the medication because of side effects. We have drawn the conclusion, that latanoprost was well tolerated.

The fact, that we observed relatively few side effects, may be partly due to the short duration of our study and the fact that inflammatory signs and symptoms of orbitopathy, such as ocular irritation, watering and eye pain might have had some masking effect on the side-effects of latanoprost.

The IOP in Graves' orbitopathy is strongly position dependent, with the tendency to elevate in up-gaze (19). We have taken care to measure IOP in the same position of the patients' head each time, to eliminate the error related to the position of the eye.

We have found out, that latanoprost, common first choice treatment for POAG and OH is effective and well tolerated in the treatment of IOP elevation secondary to Graves' disease. Further studies should address the efficacy and tolerance of other intraocular pressure lowering medications in glaucoma and ocular hypertension secondary to Graves' disease to answer the question what the best choice is.

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