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Research Protocol

Study Title

Randomized Controlled Crossover Trial Comparing Effectiveness and Tolerability of Generic and Brand Name Travoprost in Patients with Primary Open Angle Glaucoma, Normotensive Glaucoma, and Ocular Hypertension

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1. Introduction

Glaucoma is a chronic optic neuropathy and the leading cause of irreversible blindness in the world [1]. The main risk factor, and the only modifiable one, is intraocular pressure (IOP). The impact of poorly controlled IOP in a patient with glaucoma can lead to more rapid progression of the disease and blindness [2]. There are several classes of topical medication that can lower IOP, including beta-blockers, alphas adrenergic agonists, carbonic anhydrase inhibitors, and prostaglandin analogues. The most commonly prescribed first line treatment in North America remains prostaglandin analogues such as Travoprost, available since 2013 in generic form.

It should be noted that in 2006, the first formulation of Travoprost (Travatan) containing benzalkonium chloride (BAK), a very common preservative known to irritate the ocular surface, was replaced by a new formulation called Travatan Z having as its agent Sofzia, an ionic tamponade system. The mention of the original Travoprost in this project, refers to the Travatan Z since the one with BAK is no longer available.

For financial reasons, both for the patient and for society, the government promotes the development of generic drugs at a lower cost and encourages pharmacists to make transition with patients. Many patients using the original Travoprost (Travatan Z) have their treatment modified with generic Travoprost, often without the consent of their treating physician. In Canada, a generic ophthalmic drop with the same active ingredient, at the same concentration as the reference drug, is presumed to be bioequivalent, without the need for a comparative efficacy study. [3]. It is known that Latanoprost, another prostaglandin analogue, may be less stable in generic form than in its original version (Xalatan) under certain conditions. Variations in the concentration of Latanoprost and certain physicochemical properties, such as pH , the material of the container, the size of the drop distributed, are possible which can influence the bioavailability and therefore the effectiveness of the drug [4] [5] [6]. Finally, a variation of the non-medicinal ingredients between the 2 drugs may result in a difference in the type and frequency of the adverse effects, and even affect the efficacy of the product.

In terms of therapeutic efficacy and safety of care, and for reasons of health care costs, it is important to demonstrate whether there is a therapeutic equivalence between generic Travoprost and the brand Travoprost (Travatan Z).

Is this a pilot study? yes no

1a. Review of the literature

Currently, there are many controversies in the literature on the therapeutic equivalence of anti-glaucoma drops and the opinion among experts differ.

Ophthalmic drop may not be as effective as the reference drug, as the efficacy of the generic drug does not need to be proven for market entry in Canada [3].

IOP may be less well controlled with generic Latanoprost, due to variations in the physicochemical properties of the solution, including Latanoprost concentration. These variations are due, among other things, to the properties of the bottle used or the non-medicinal ingredients that differ from the reference medicine [4][5][6][7].

A 2007 study by Narayanaswamy et al. demonstrated a difference between the generic and original versions of Latanoprost. This pilot study involving 30 patients in a single center in India seemed to demonstrate that generic Latanoprost was less effective than Xalatan in lowering IOP. [8]. However, this is only a small study and some questions about the reliability of the results have surfaced, including concerns regarding the improper storage of the generic Latanoprost used.

On the other hand, several studies have shown an equivalence between the generic drug and the original. A randomized, double-blind study in 2011 by Diguini et al., involving 184 patients, demonstrated the non-inferiority of a generic version of Latanoprost compared to Xalatan.[9]. On the other hand, the generic version used in this study had a composition qualitatively and quantitatively identical to Xalatan, which is often not the case [4][10]. Another randomized multicentre study, by Allaire et al., included 266 patients with diagnosis of primary open angle glaucoma and ocular hypertension. Each patient was assigned to the generic Latanoprost group or the Xalatan group in a ratio of 1: 1. This study demonstrated therapeutic equivalence as well as the same safety profile [11]. Finally, a randomized crossover study by Golan et al. in 2015, compared Glautan, a generic version of Latanoprost, to Xalatan in 19 patients. The hypotensive effect and ocular side effect profile was comparable [12].

2. Objectives

The primary goal was to determine if generic Sandoz-Travoprost is as effective as brand Travatan Z in lowering intraocular pressure, as measured using Goldmann applanation tonometry.

The secondary goal was to determine if patients tolerate generic Sandoz-Travoprost as well as brand Travatan Z, using a questionnaire.

3. Methodology

a. Study Design

Randomized controlled clinical trial, unblinded, crossover trial.

The crossover design was chosen to achieve the power required all the while limiting the number of patients required.

This study was not blinded to reproduce as much as possible the real situation experienced in clinic by the patients and the doctors. The use of masked bottles by the pharmacy was considered. However, some studies have suggested that the different characteristics of drop bottles may have an impact on the size of the drop or the concentration of the drug after 30 days[14]. So it was decided to use the original bottles.

b. Information on the medication used in the study [15]

The two drugs in the study are the original Travoprost (Travatan Z) and the generic Travoprost. Both are approved in Canada for hypotensive therapy in patients with GPAO or HTO. They are available in solution in 5 mL bottles. Since there are several companies that produce generic Travoprost, we would choose a version that will be the same for the entire study.

i. Mechanism of action:

Selective FP prostanoid receptor agonist that decreases intraocular pressure by increasing uveoscleral drainage.

ii. Posology and administration:

The recommended dosage is a drop in the affected eye or eyes once a day. The optimal effect is obtained by administering it in the evening. The instillation rate of Travatan Z ophthalmic solution (Travoprost) should not exceed 1 time / day, as it has been demonstrated that a higher frequency may decrease the reducing effect of intraocular pressure.

The reduction in intraocular pressure begins approximately 2 hours after instillation and reaches its maximum after 12 hours.

Storage between 2 ° C and 25 ° C recommended for stability.

iii. Ingredients:

Active ingredient: Travoprost 0.040mg/mL

Other ingredients: Sofzia (preservation system with boric acid, propylene glycol, sorbitol, zinc chloride), polyoxyethylenated hydrogenated castor oil 40 and purified water. A very small amount of hydrochloric acid or sodium hydroxide is added to maintain the pH at the appropriate value.

iv. Ocular adverse effects

> 10% :

Changes affecting eyelashes such as increased eyelash length and increased eyelash thickness (61%), ocular hyperaemia (30-50%)

1% to 10% :

Decreased visual acuity (5% to 10%), ocular discomfort (5% to 10%), eye pain (5% to 10%), eye pruritus (5% to 10%), blepharitis (1% to 4%), impaired vision (1% to 4%), cataracts (1% to 4%), conjunctivitis (1% to 4%), corneal staining (1% to 4%), crusting eyelids (1% to 4%), dry eye syndrome (1% to 4%), eyelid hyperpigmentation (periorbital, 1% to 4%), hyperpigmentation of the iris (1% to 4%), keratitis (1% to 4%), tearing (1% to 4%), ophthalmic inflammation (1% to 4%), photophobia (1% to 4%), subconjunctival hemorrhage (1% to 4%)

Post-marketing and / or case reports :

Bacterial keratitis (due to contamination of solution), corneal edema, cystoid macular edema, iritis, macular edema

v. Systemic adverse effects

> 10% :

None reported

1% to 10% :

Cardiovascular: angina pectoris (1% to 5%), bradycardia (1% to 5%), chest pain (1% to 5%), hypertension (1% to 5%), hypotension (1% to 5%)

Central nervous system: Anxiety (1% to 5%), depression (1% to 5%), headache (1% to 5%), pain (1% to 5%)

Dermatological: hyperpigmentation of eyelashes, increased growth of eyelashes

Endocrine and metabolic: hypercholesterolemia (1% to 5%)

Gastrointestinal: dyspepsia (1% to 5%), gastrointestinal disorders (1% to 5%)

Genitourinary: prostate disease (1% to 5%), urinary incontinence (1% to 5%), urinary tract infection (1% to 5%)

Hypersensitivity: Hypersensitivity Reactions (1% to 5%)

Infection: Infection (1% to 5%)

Neuromuscular and skeletal: arthritis (1% to 5%), back pain (1% to 5%)

Respiratory: Bronchitis (1% to 5%), flu-like symptoms (1% to 5%), sinusitis (1% to 5%)

Post-marketing and / or case reports :

Asthma, tachycardia

vi. Contraindications

Allergy to prostaglandin analogues or any of the other ingredients of the product

Being pregnant or considering pregnancy (Risk Factor C for pregnancy)

vii. Interactions

Non-steroidal anti-inflammatory drug: may increase the therapeutic efficacy of prostaglandins

viii. Pharmacodynamics and pharmacokinetics

Start of action: 2 hours

Maximum effect: 12 hours

Half life: 45 minutes

ix. Inactivation and elimination

Inactivation by the kidneys, liver and lungs.

4. Study population

a. Target population:

All adult patients with primary open angle glaucoma, normotensive glaucoma, or ocular hypertension requiring pharmacological treatment seen at CHUS.

5. Sample size and inclusion / exclusion criteria

The calculation of the sample size is based on a paired t test, assuming a normal distribution of intraocular pressure. To demonstrate an equivalence between Travoprost original (Travatan Z) and generic Travoprost, a sample size of 69 patients will be required. This will detect a difference of 1.5mmHg with a power of 80% and an alpha of 0.05, assuming a standard deviation of 3.5mmHg. Assuming a loss at follow-up of 10%, the required number of patients is 76.

a. Inclusion criteria

- To be of age
- Be able to consent and sign the consent form
- Have a diagnosis of primary open angle glaucoma, normotensive glaucoma, or ocular hypertension requiring pharmacological treatment

b. Exclusion criteria

- Angle closure glaucoma
- Having had laser iridotomy
- Allergy known to Travatan or Travaprost, or to any other components of the products
- Use of other hypotensive ophthalmic drops (except for Travatan Z or generic Travoprost)
- Use of corticosteroid
- To be pregnant
- Breast-feed
- Being monocular
- Have had glaucoma surgery such as trabeculectomy and Tube implants (eg Baerveldt, Ahmed). Patients who have had selective laser trabeculoplasty will also be excluded.
- Active intraocular inflammation
- Ocular surface disease that may interfere with an accurate measurement of IOP
- Any clinically significant eye disease that may interfere with the study

6. Recruitment

The subjects will be adult patients seen in the outpatient ophthalmology clinic of the Hotel-Dieu de Sherbrooke, who require or already use a pharmacological treatment of Travoprost original (Travatan Z) or generic Travoprost and meeting the eligibility criteria.

The subjects will be recruited at the outpatient ophthalmology clinic of the Hôtel-Dieu de Sherbrooke after a new consultation or a follow-up appointment. The physician resident will present the study to the patient, complete the consent form and obtain their signature.

The randomization will be done beforehand.

The only inconveniences for patients, no matter what group they are in, are the 2 follow-up visits, one to 3 weeks and one to 6 weeks.

7. Variables and data collection

Variable	Type	Method of measurement
age	continuous	From the chart
sex	dichotomous	From the chart

ethnic group	categorical	From the chart
diagnostic	categorical	From the chart
IOP	continuous	Goldmann applanation tonometry
initial treatment	dichotomous	From the chart
MD (visual fields)	continuous	Visual field; at the initial appointment
side effects	dichotomous	questionnaire; at the 3 week and 6 week appointments
treatment adherence (number of days missed)	continuous	questionnaire; at the 3 week and 6 week appointments

The data will be collected by the resident in charge of the project, who will be responsible for their management. Registration will be in accordance with the accepted standards of confidentiality as described in the Act respecting health services and social services.

We will use the Goldmann tonometer, a device on the slit lamp, to measure intraocular pressure. Currently, she is the gold standard for measuring intraocular pressure[13].

The questionnaire given to patients will be a home-based questionnaire designed to check whether patients have had difficulty putting the drops, if they forget to put them on and if they have had adverse effects. The questionnaire will contain a list of side effects that patients can easily identify. The questionnaire will be filled verbally with the patient, and not just read and checked.

The mean deflection index (MD), a parameter given by the automated visual field, is an accepted measure in the literature for stratifying the glaucoma stage, either mild, moderate, or advanced [13].

8. Study Protocol

a. For patients who are new consultations:

At the first visit, the patient's sociodemographic data will be collected and a complete ophthalmic examination will be performed. This examination will include visual acuity, external examination, evaluation of the cornea, anterior chamber, iris, lens, vitreous, retina and optic nerve (with pharmacological dilatation). Intraocular pressure, gonioscopy, pachymetry and visual field Humphrey SITA fast 24-2. If the patient qualifies for the study, resident David Ta Kim will present the study. If the patient agrees, resident David Ta Kim will complete the consent form with the patient and get his signature. The patient will receive a bottle of original Travoprost (Travatan Z) or generic Travoprost according to the prior randomization. The patient will receive explanations on how to apply the drops.

During the second visit, at 3 weeks +/- 3 days, the IOP will be taken by resident David Ta Kim at 9:00 +/- 1h. A bottle of the other medicine will be given to him.

At the third visit at 6 weeks +/- 3 days, the IOP will be taken by resident David Ta Kim at 9:00 +/- 1h. The patient will have completed the study and a prescription from Travoprost will be given.

A questionnaire on tolerance and comfort of drops will be completed with the patient at the second and third visit.

b. For patients who were already followed and treated with brand Travoprost (Travatan Z) or generic Travoprost:

At the follow-up visit, if the patient qualifies for the study, resident David Ta Kim will present the study. If the patient agrees, resident David Ta Kim will complete the consent form with the patient and get his signature. The sociodemographic data of the patient will be collected and a complete ophthalmological examination will be performed. This examination will include visual acuity, external examination, evaluation of the cornea, anterior chamber, iris, lens, anterior vitreous, retina and optic nerve (with pharmacological dilatation). Intraocular pressure, gonioscopy, pachymetry and visual field Humphrey SITA Standard 24-2. Gonioscopy, pachymetry and the visual field could be delayed if they were done in the previous 4 months. The patient will receive a bottle of original Travoprost (Travatan Z) or generic Travoprost according to the prior randomization. The patient will receive explanations on how to put the drops.

During the second visit, at 3 weeks +/- 3 days, the IOP will be taken by resident David Ta Kim at the same time as the first visit +/- 1h. A bottle of the other medicine will be given to him.

At the third visit at 6 weeks +/- 3 days, the IOP will be taken by resident David Ta Kim at the same time as the first visit +/- 1h. The patient will have finished the study and a prescription of his starting medication will be given.

A questionnaire on tolerance and comfort of drops will be completed with the patient at the second and third visit.

c. For patients who drop out of the study or who are lost to follow-up:

A loss of follow-up of 10% is anticipated so the sample size has been increased by 10%.

d. Management of adverse effects:

The adverse effects of these drugs are well known and are mostly minor and transient. A questionnaire on tolerance and comfort of drops will be completed with the patient at the second and third visit. If, however, a patient is very concerned about an adverse reaction, they may contact the ophthalmology outpatient clinic or contact the resident on call.

Table: Summary of 3 visits by group

	Recruitment day (day 0)	Second visit (at 3 weeks)	Third visit (at 6 weeks)
Group 1 (new randomized consultation to receive Travatan Z first)	<ul style="list-style-type: none"> • Presentation of the study to the patient • Obtaining consent • Taking of IOP • A bottle of Travoprost original (Travatan Z) given with instructions to instill a drop at bedtime in the eye reaches 	<ul style="list-style-type: none"> • IOP taken by the resident • Complete the questionnaire on the comfort of the treatment • A bottle of generic Travoprost given with instruction to instill a drop at bedtime in the eye reaches 	<ul style="list-style-type: none"> • IOP taken by the resident • Complete the questionnaire on the comfort of the treatment • End of the study
Group 2 (New Randomized Consultation to Receive Generic Travoprost First)	<ul style="list-style-type: none"> • Presentation of the study to the patient • Obtaining consent • A bottle of generic Travoprost given with instruction to instill a drop at bedtime in the eye reaches 	<ul style="list-style-type: none"> • IOP taken by the resident • Complete the questionnaire on the comfort of the treatment • A bottle of Travoprost original (Travatan Z) given with instructions to instill a drop at bedtime in the eye reaches 	<ul style="list-style-type: none"> • IOP taken by the resident • Complete the questionnaire on the comfort of the treatment • End of the study

<p>Group 3 (Patient already randomized to receive Travatan Z first)</p>	<ul style="list-style-type: none"> • Presentation of the study to the patient • Obtaining consent • A bottle of Travoprost original (Travatan Z) given with instructions to instill a drop at bedtime in the eye reaches 	<ul style="list-style-type: none"> • IOP taken by the resident • Complete the questionnaire on the comfort of the treatment • A bottle of generic Travoprost given with instruction to instill a drop at bedtime in the eye reaches 	<ul style="list-style-type: none"> • IOP taken by the resident • Complete the questionnaire on the comfort of the treatment • End of the study
<p>Group 4 (Patient already randomized to receive generic Travoprost first)</p>	<ul style="list-style-type: none"> • Presentation of the study to the patient • Obtaining consent • A bottle of generic Travoprost given with instruction to instill a drop at bedtime in the eye reaches 	<ul style="list-style-type: none"> • IOP taken by the resident • Complete the questionnaire on the comfort of the treatment • A bottle of Travoprost original (Travatan Z) given with instructions to instill a drop at bedtime in the eye reaches 	<ul style="list-style-type: none"> • IOP taken by the resident • Complete the questionnaire on the comfort of the treatment • End of the study

9. Data analysis

The database will be created with Microsoft Excel.

Statistical calculations will be done with SPSS v20.

a. Comparison of the composition of the different groups

A t-test will be used for continuous variables (if the data are not normally distributed, a Mann-Whitney test will be used).

A Chi-square test will be used for categorical variables (if the frequency is less than 5 for a variable, an exact Fisher test will be used).

b. Comparison of groups at the end of the study

A paired t test will be used if the data is normally distributed (otherwise, a Wilcoxon test will be used).

c. Analysis of the therapeutic effect of drugs

An ANOVA test will be used to compare the effect of the treatments over time (an appropriate transformation will be applied to the data if it is not normally distributed).

d. Comparison of adverse effects between the two treatments

A McNeman test will be used to see if each side effect is as common with both treatments.

e. Comparison of compliance with each treatment

A paired t test will be used to see if patients have the same compliance for each treatment (Wilcoxon test if non-normal data).

10. Limitations

There is a potential bias of information if a patient believes that the generic is less effective, which could lead to a decrease in compliance or a change in dosage by the patient (eg: he could put it twice a day and not once). To counter this bias, the importance of abiding by the prescribed posology will be explained to patients.

To avoid a learning bias, patients who start topical treatment for the first time will be told how to instill the drops during the initial outpatient visit. This instruction will be given by the resident to show the correct way to instill eye drops. A practice will then be performed using a new bottle of artificial tears. For those who are already taking Travoprost (Travatan Z) or generic Travoprost, they will be asked, during their first outpatient visit, to demonstrate how they instill their gout using a new bottle of artificial tears. If necessary, they will receive a short lesson given by the resident.

The loss to follow-up, inevitable in a prospective study, would lead to an information bias. The sample size has therefore been increased by 10%.

11. Ethical considerations

Adverse effects related to the use of Travoprost, as well as the patient's required time and movement, are the only real disadvantages. Follow-up will be provided by the treating team.

12. Anticipated benefits

With the information obtained as to the equal or lesser effectiveness of generic Travoprost compared to the original Travoprost (Travatan Z), we will be able to better inform patients asking if the generic version of their ophthalmic drop is equivalent reference drug. If we find equal efficiency, the savings could be remarkable. However, if we find less efficiency, then we

can ensure that the Travoprost served to our patients is the original Travoprost (Travatan Z) and not a generic, ensuring better control of IOP and therefore better control of the disease.

13. Dissemination of results

We hope to publish the results of this study in a specialized journal in ophthalmology and present them at local, national and international conferences. The results could also be communicated to pharmacists, to raise awareness of the effectiveness (or lack of effectiveness) of generic Travoprost.

14. Schedule

2015/08 Submission to the Scientific and Ethics Committees

2016/07 Start of patient recruitment

2017/07 Data analysis

2017/10 Writing and publication of the article

15. Budget

The cost of the study will be solely due to the ophthalmic drops delivered to patients.

Sample size:	69
Loss to follow-up:	10%
Increased sample size to compensate for anticipated loss to follow-up:	76
Cost per bottle of generic Travoprost (5mL):	\$44.99
Cost of generic Travoprost with taxes	\$51.74
Bottles of generic Travoprost per patient	1
Total per patient (including taxes):	\$51.74

Total cost of Travoprost:	\$3,926.95
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Source of funding:

1. CHUS Department of Surgery Research Bursary Award: \$ 4000
2. For the brand Travoprost (Travatan Z), excess unexpired samples in the clinic will be used
3. No pharmaceutical company funding will be used

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