Genetic association study on corticosteroid-induced elevation of the intraocular pressure

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The objective is to investigate the differences in SNPs in patients with corticosteroid-induced ocular hypertension in comparison with patients exposed to corticosteroids who do not respond with an IOP increase. Based on the SNPs, genes involved in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glaucoma and ocular hypertension
Study type	Observational invasive

Summary

ID

NL-OMON47660

Source
ToetsingOnline

Brief title
Gene polymorphisms of corticosteroid responders

Condition

- Glaucoma and ocular hypertension

Synonym
corticosteroid responder, Corticosteroid-induced glaucoma

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: - Corticosteroid-induced ocular hypertension/glaucoma, - Gene polymorphisms, - Glucocorticoids, - Ophthalmology

Outcome measures

Primary outcome

The primary objective is to investigate the differences in SNPs in patients

with corticosteroid-induced ocular hypertension in comparison with patients

exposed to corticosteroids who do not respond with an IOP increase. This can be

obtained with a one-time peripheral blood sample.

Secondary outcome

Not applicable.

Study description

Background summary

Glaucoma is one of the most prevalent eye diseases and the second most common cause of blindness worldwide. The most common form is primary open angle glaucoma (POAG). Glaucoma is a slowly progressing neuropathy of the optic nerve that causes loss of visual field and eventually blindness. Elevated intra-ocular pressure (IOP) is the most important risk factor.

Corticosteroids, which are often used for the treatment of many diseases in ophthalmology and other specialities, may cause an elevation of the IOP. The chance of an elevation of the IOP is highest with topical, subtenon, subconjunctival and intravitreal administration. However, also dermal, nasal, inhalant and systemic use of corticosteroids may cause an elevation of the IOP. When this happens, it is called a steroid response. It is estimated that corticosteroids induce ocular hypertension in approximately 18%-36% of the general population and in patients with POAG this percentage can be as high as 92%. The elevated IOP is mostly reversible when the use is terminated, but it may take some time to normalize. However, when the treatment is sustained, this can cause a glaucomatous neuropathy of the optic nerve. The latter is called corticosteroid-induced glaucoma and may lead to visual field loss and eventually blindness.

The IOP is determined by the outflow resistance across the trabecular meshwork and the Schlem-canal system, the aqaeous humour production and the level of episcleral venous pressure. Corticosteroid-induced glaucoma is caused by an increase in outflow resistance. However, the precise mechanism isn*t clear yet. Genetic factors are likely to affect the susceptibility to a corticosteroid response. Therefore, an overview of the genetic and molecular mechanisms of corticosteroid-induced glaucoma can give more insight in the pathogenesis. Genetic association studies give us the opportunity to discover genes that are associated with the disease by searching for variances in alleles or genotypes (SNPs or single nucleotide polymorphisms) in the genomes between patients with and without IOP response on corticosteroids.

In this study we will investigate the occurrence of SNPs in around 125 cases with corticosteroid-induced ocular hypertension in comparison with around 235 controls without a corticosteroid response. In order to find SNPs related to the corticosteroid response, it is important that both groups are comparable by means of underlying disease. Therefore, patients will be matched on the indication for the use of corticosteroids, the duration of exposure, route of administration, and type and dosage of the corticosteroid.

To our knowledge one small genome-wide association study (GWAS) has been conducted comparing 32 patients with and without corticosteroid-induced ocular hypertension after treatment with intravitreal triamcinolone. They identified two SNPs proximal of the transcriptional start site (near the 5*) of HCG22 on chromosome 6, suggesting that the molecular mechanisms for association of the variants with IOP could be through the regulation of the HCG22 gene expression. However, this is a rather small sample population and the investigators didn*t match for the underlying disease. Further, Hogewind et al. performed SNP analysis in multiple genes (SFRS3, FKBP4, FKBP5, and NR3C1) in corticosteroid-induced ocular hypertension.

This study enables us to identify patients at risk for developing corticosteroid-induced glaucoma and to gain a better insight in the pathogenesis of corticosteroid-induced glaucoma. This may also lead to the discovery of biomarkers that indicate an increased risk of developing steroid-induced glaucoma and new prevention and treatment strategies, which are necessary as the treatment of corticosteroid induced glaucoma now only focuses at lowering the IOP and can still be challenging.

Study objective

The objective is to investigate the differences in SNPs in patients with corticosteroid-induced ocular hypertension in comparison with patients exposed to corticosteroids who do not respond with an IOP increase. Based on the SNPs, genes involved in corticosteroid-induced glaucoma can be identified.

Study design

This study is an observational cohort study (matched case-referent) and will be conducted at the University Eye Clinic Maastricht of the Maastricht University Medical Centre+ (MUMC+), the Netherlands. Patients will be included from the outpatient clinic. The study population will consist of patients that are using or have recently used topical, subconjunctival or intravitreal corticosteroids. The participants will be divided in two groups: cases of corticosteroid responders and controls without a corticosteroid response. A corticosteroid response will be defined as an increase of the IOP * 6 mmHg from baseline and in comparison to the other eye (in case of unilateral treatment). Patients who have shown an increase in IOP after exposure to corticosteroids will be identified as reported by the treating ophthalmologist or resident in the medical record. Referents will be identified as those who have been exposed to corticosteroids but didn*t have an increase in IOP.

As previously described, patients will be matched based on their indication for the use of corticosteroids, the duration of exposure, route of administration, and type and dosage of the corticosteroid. In order to perform the matching, the inclusion of the patients will be checked weekly and we will make sure that for every patient with a corticosteroid response, two patients without a response will be found.
Previous studies showed that on average, one out of three patients develop an increase in intraocular pressure after using topical corticosteroids and two out of three don*t. The matching will be ensured as all patients that are exposed to corticosteroids will be included.

The clinicians will identify their patients who, based on their data in the clinical patient system (SAP), may qualify for participation in this study. This identification will take place over a retrospective period of six years (to 2010). After identification, the treating clinicians will send their patients a noncommittal letter in which they inform the patient about this study. The patient information and informed consent will hereby be attached. If patients are willing to participate they are asked to contact the researcher before the start of their appointment and are asked to bring the informed consent with them. During the appointment, the clinician will also ask whether the patient has received the letter and if he/she wants to be approached by the researcher. During the consultation hours, the researcher will be available to provide further details about this study, to include patients if they wish to participate and to sign the informed consent.
Further, the treating clinicians will identify new corticosteroid responders and patients that are newly exposed to corticosteroids (in the context of the matching) during their regular consultation hours. These patients will be informed about this study by their own treating clinician and they will receive the patient information letter. Patients will also be asked if they, free of any obligation, want to be approached by the researcher. In case of agreement,

the researcher will contact the patient after one week. If patients are willing to participate, an appointment will be planned (if possible adjacent to another planned appointment). The patients will also be asked to bring the informed consent letter they have received to the scheduled appointment. The informed consent will be signed together with the researcher.

The duration of inclusion is estimated at one to one and a half years and the duration of the study at two years.

Study burden and risks

The risks associated with participation are negligible and the burden can be considered minimal. The blood collection may cause some pain and a bruise. The blood sample will provide three tubes of 10 ml blood within one venous bloodpunction (in total 30 ml) and is unlikely to cause other complaints.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age > 18 year and mentally competent
- Patient from the Maastricht University Medical Centre + (MUMC+), the Netherlands
- Use of corticosteroids:
* Patients treated with Ozurdex (an intravitreal dexamethasone implant)
* Patients treated with subconjunctival Triamcinolone/ Celestone injections
* Patients treated with corticosteroids after a corneal surgery
* Patients treated with corticosteroids after a refractive surgery
* Patients treated with corticosteroids after a cataract surgery
* Patients treated with corticosteroids for macular edema
* Patients exposed to corticosteroids for other diseases such as uveitis
- In case of surgery, time after surgery * 3 months

Exclusion criteria

- Age < 18 year
- Mentally not able to participate or to give permission
- Not able to communicate in Dutch
- Patients with a type of uveitis that might cause a decrease of the IOP
- In case of surgery, time after surgery < 3 months

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-09-2017
Enrollment:	370
Type:	Actual

Ethics review

Approved WMO Date:	20-04-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL58992.068.17