A SYSTEMS BIOLOGY APPROACH TO OCULAR INFLAMMATION

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Ocular infections, irritations and inflammations
Study type	Observational non invasive

Summary

ID

NL-OMON55622

Source
ToetsingOnline

Brief title
Systems biology in ocular inflammation

Condition

- Ocular infections, irritations and inflammations

Synonym
ocular inflammation, uveitis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Dr. F.P. Fischerstichting;St. Lijf en Leven;Stichting Ankie Hak;Rotterdamse Stichting Blindenbelangen;LSBS;Vrienden van het UMC,MedImmune

Intervention

Keyword: age related macular degeneration, inflammatory corneal disease, orbital inflammatory diseases, scleritis, strabismus, systems biology, uveitis

Outcome measures

Primary outcome

the networks acquisition of high throughput analyses of distinct layers (e.g.

mRNA, microRNA, methylation status, proteome) and various cellular subsets

(e.g. B cells, T cells, dendritic cells, NK cells)

Secondary outcome

na

Study description

Background summary

Ocular inflammation is a chronic, progressive and degenerative inflammation of any or all compartments of the eye including the uveal tract (uveitis and age-related macular degeneration), the cornea and orbita and cause an immediate threat to vision. The pathogenesis of ocular inflammation is poorly understood. Current treatment strategies include various immunosuppressive medications but fail to prevent or stop the decline in visual function, and usually induce many adverse effects that affect quality of life, as immunosuppressant therapy is often life-long. Hence, further research to understand pathogenesis and improve prognosis for these patients is highly justified. Systems biology is an interdisciplinary approach that systematically describes the complex interactions between all the parts in a biological system, with a view to elucidating new biological rules capable of predicting the behavior of the biological system. To this aim, data are collected from all the components of a biological system, analyzed and integrated in order to generate a mathematical model that describes or predicts the response of the system to individual perturbations.

Study objective

Systems biology is an interdisciplinary approach that systematically describes the complex interactions between all the parts in a biological system, with a

view to elucidating new biological rules capable of predicting the behavior of the biological system. To this aim, data are collected from all the components of a biological system, analyzed and integrated in order to generate a mathematical model that describes or predicts the response of the system to individual perturbations. To delineate these networks acquisition of high throughput analyses of distinct layers (e.g. mRNA, microRNA, methylation status, proteome) and various cellular subsets (e.g. B cells, T cells, dendritic cells, NK cells) that constitute the network is obligatory. Due to the integration of all the biological information using high throughput technology, molecular signatures that typify different forms and disease activity of intraocular inflammation will be identified and provide novel therapeutic targets.

We aim to employ an *omics*-driven systems biology approach on patients with ocular inflammation in order to identify the molecular pathways underlying the pathogenesis and develop clinically useful markers to predict disease outcome and treatment responses. Decipher the molecular pathways that underlie intraocular inflammation.

1. To investigate the frequency, function and phenotype of circulating immune cells; T cells, B cells, plasmacytoid dendritic cells, monocytes, and NK cells. Plasma and serum will be collected to measure the circulating cytokines using Luminex and the immune cells will be isolated. The surface markers and the intracellular cytokine production of these cells will be analyzed by flow cytometry. The T cells, pDCs and monocytes will be cultured and after stimulation the supernatants will be analyzed by Luminex, the gene expression of the cells will be investigated by qPCR.
2. To investigate the transcriptome and epigenome of circulating immune cells by RNA sequencing miRNA profiling and genome-wide methylation of cell subsets.
3. To identify, using high throughput technology, molecular signatures that typify different forms and disease activity of intraocular inflammation.

Study design

This study is designed as an observational cross-sectional study for the duration of 4 years. For the present study we will recruit patients with uveitis, corneal disease and age-related macular degeneration at the outbound department of ophthalmology. We estimate (on the basis of the current flow of new patients that we will be able to include 630 patients with uveitis (anterior uveitis (n=60), intermediate uveitis (n=60) posterior uveitis (n=60), panuveitis (n=60) and scleritis (n=60)), age-related macular degeneration (n=60), retinal dystrophy (n=60), multifocal choroidal retinitis (n=60), inflammatory corneal disease (n=40), orbital inflammatory diseases and lymphoma (n=60), and strabismus (n=30). From this cohort and for the purpose of the current study proposal, patients with ocular inflammation will be asked for a blood sample (ranging between 11mL and 81mL total blood, dependent on age). A venipuncture is performed to obtain a certain amount of blood dependent on age:

- Age of 0-6: a total of 11 mL blood; 6 mL EDTA blood for plasma samples and 5 mL clotting blood for collection of serum or 9 mL Lithium Heparin or Sodium Heparin blood and 2 mL clotting blood.
- Age of 7-15: a total of 29 mL blood; 27 mL Lithium Heparin or Sodium Heparin blood and 2 mL clotting blood.
- Age of 16 and above: a total of 81 mL blood; 70 mL Lithium Heparin or Sodium Heparin blood for investigating the circulating immune cells using flow cytometry, luminex and qPCR, 6 mL EDTA blood for collection of plasma and 5 mL clotting blood for collection of serum.

Blood drawn from the study patients enters the Radstake lab after which various immune cell subsets will be carefully isolated (B, T and NK cells, myeloid DCs, plasmacytoid DCs and monocytes) for the determination of the transcriptome (RNA sequencing) and epigenome (miRNA profiling and genome-wide methylation). Simultaneously, these cell subsets will be phenotypically analyzed employing extensive flow cytometry protocols. Besides the regulation at the cellular level, we will study the circulatome by exploiting the Luminex core facility (UDAIR) present in our lab. UDAIR is optimized to measure ~ 150 cytokines / chemokines / growth factors in small sample volumes (50 ul). In addition, we will study the level of oxidative stress markers and the presence of inflammatory lipids at the fentomolar level in collaboration with our metabolomics facility. Both UDAIR and the metabolomics facility enable us to study the circulatome and merge this data with what we see on the cellular level thereby identifying causative pathways / circulating markers of relevance.

Study burden and risks

The risks of a venepuncture are generally considered to be very low. It is possible that a haematoma develops at the venepuncture site. The risks of topical mydriatics are considered low. After administration, the patient may experience a blurry vision and a sensation of photophobia. Topical mydriatrics will not be given to patients who are pregnant or are breastfeeding or have a high(er) chance of developing glaucoma. Flare measurements are conducted during the regular ophthalmic examination. The side effects are nil. Patients can have short-term complaints of afterimages.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

Patients aged under 96 years old diagnosed with ocular inflammation:
- uveitis; anterior uveitis, intermediate uveitis, panuveitis, scleritis and posterior uveitis
- inflammatory corneal disease (keratokonus or Fuchs endothelial corneal dystrophy)
- inflammatory orbital disease and orbital lymphoma
- Age-related macular degeneration
- Retinal dystrophy
- Multifocal choroidal retinitis
- Strabismus

Exclusion criteria

- Patients with acquired immune deficiencies will not be eligible for participation.
- Patients who do not speak or understand the Dutch language adequately will also be excluded from participation in this study
- Current effective use of systemic immunomodulatory agents (antimetabolites), biologicals or cyclosporine.
-IV corticosteroids in the last 14 days for inclusion
-Age >=96 years

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-07-2014
Enrollment:	630
Type:	Actual

Ethics review

Approved WMO Date:	21-05-2014
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-07-2014
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	01-10-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-02-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-02-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-11-2019
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	20-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	METC NedMec

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	NL46874.041.13

Study results

Results posted: 03-04-2023

Summary results
Trial ended prematurely

First publication
01-01-1900