MONOPOLY: predicting clinical benefit of dupilumab in adult patients with chronic rhinosinusitis with nasal polyps (CRSwNP)

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Primary objective: to identify predicting phenotypical and endotypical biomarkers for the response to dupilumab in adult patients with CRSwNP, by comparing the type 2 inflammation in the peripheral blood and nasal polyp tissue at baseline and after…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Upper respiratory tract disorders (excl infections)
Study type	Observational invasive

Summary

ID

NL-OMON54163

Source
ToetsingOnline

Brief title
Dupilumab in patients with CRSwNP

Condition

- Upper respiratory tract disorders (excl infections)

Synonym
chronic rhinosinusitis with nasal polyps; CRSwNP

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: biological, dupilumab, polyps, rhinosinusitis

Outcome measures

Primary outcome

Histochemical and single cell suspension flow cytometry analysis

Secondary outcome

does not apply

Study description

Background summary

Chronic rhinosinusitis (CRS) is a global commonly prevalent disease negatively effecting the quality of life of patients and with a significant burden on society in terms of healthcare consumption and productivity loss. Traditionally CRS is dichotomously classified by phenotype, either with or without nasal polyps (respectively CRSwNP and CRSsNP). The last decades gave rise to a paradigm-shift, with a focus on the underlying endotype driven immunopathophysiology. Besides dominating the current basic research on this topic, the endotype perspective increasingly seeps into clinical practice, with new current and future treatment possibilities coming to light. In Western countries, CRSwNP is a mainly type-2 inflammatory driven morbidity, involving IL-4, -5, -9 and -13. Human monoclonal antibodies (hMABs, also called biologicals) directed against the cytokines involved have proven effective in other, often related, type-2 driven pathologies, such as asthma, atopic dermatitis and eosinophilic esophagitis. Dupilumab is one of such hMABs, directed against IL*4Rα, a component shared by the IL-4 and IL-13 receptors. By inhibiting IL*4R signaling of both IL*4 and IL*13 it effectively downregulates the molecular pathways that drive the type-2 inflammation. As of 2019, dupilumab has been approved in Europe and the US for the treatment of CRSwNP with type-2 inflammation. The prefacing phase 2 and 3 trials showed dupilumab to be safe and mostly clinically effective, although 10% of patients appeared non-responding to the treatment. It is yet unknown if this number corresponds with the regular care setting. Importantly, these studies did not investigate phenotypical or endotypical biomarkers to predict clinical response to this new and expensive treatment option. This is paramount for improving future

indication assessment and clinical monitoring of dupilumab in the treatment of patients with CRSwNP, enabling precision medicine and optimizing health-care efficiency. By defining such biomarkers, more insight will also be gained into the underlying immunopathophysiologic mechanisms of CRSwNP and the involved endotypes.

Additional for amendment 1:
a) less patients are non-responsive to dupilumab in our real-world observational cohort than calculated and expected from the preceding clinical trials. This is probably due to the stricter indication criterion applied as towards dupilumab*s underlying pharmacological mechanism, being proven Type-2 endotype, in our cohort; we hereby adhere to the currently ruling European guideline, EPOS2020. As such, research specimens can be obtained by biopsy on baseline, but hardly after six months of treatment, impeding comparison between the clinically distinguishable groups of (very) fast responders and (very) slow / non-responders. An additional nasal cyto-brush, with only mild discomfort and no additional risk for the patient, at baseline and six months after treatment initiation can amend this issue.

b) dupilumab is known to cause (temporary) rise of serum eosinophils. Per interim analysis of provisional study data we found patients with initial serum eosinophilia of >= 1.0 x 109/L to be of increased risk of serum eosinophil levels of >= 1.5 x 109/L, necessitating intensified blood checks every two weeks, and adapted dosing frequency when eosinophil levels of >= 3.0 x 109/L are met due to cautiousness for hypereosinophilic syndrome (HES), complicating treatment and possibly necessitating treatment cessation in case of persisting (hyper)eosinophilia (as for now +/- 1% of total treatment cohort). We want to gain insight into these dynamics, evaluate the proportionality of active/inactive eosinophils to assess the chance of developing HES, and evaluate possible biomarkers for (persisting) (hyper)eosinophilia. This can be obtained by performing the regular phlebotomy in patients with initial eosinophilia of >= 1.0 x 109/L at week 4 and 12 by our research nurses instead of by the clinical laboratory and taking 1 x 10mL blood extra per person per moment (thus total extra 2 x 10 mL); the total amount of phlebotomies is unchanged and it saves the patients time otherwise spent visiting the clinical laboratory.

Additional for amendment 2:
in daily practice the dupilumab treatment is tapered from 24 weeks onward. Every >=24 weeks the interdose interval of dupilumab is prolonged with 2 weeks, conditional to adequate treatment response and CRS-control, as defined by EPOS2020. This reduces the patients* treatment burden and reduces the direct costs related to dupilumab purchase. Intermediate evaluation demonstrates general feasibility up to interdose intervals of 6 - 8 weeks. Advanced tapering hereafter demonstrates heterogeneous results. We want to evaluate (predictive) biomarkers for the maximal interdose interval. This will eventually benefit patient centered care and gain further insight into underlying pheno- and

endotypes.

Study objective

Primary objective: to identify predicting phenotypical and endotypical biomarkers for the response to dupilumab in adult patients with CRSwNP, by comparing the type 2 inflammation in the peripheral blood and nasal polyp tissue at baseline and after 6 months of treatment with dupilumab between responders and non-responders, and between clusters of maximally tapered interdose interval.
Secondary objective: defining phenotypical differences in the peripheral blood and nasal polyp ILC2s, eosinophils, basophils, and mast cells between responders and non-responders to dupilumab, and between clusters of maximally tapered interdose interval.

Study design

Open prospective observational study with consecutive patient inclusion

Study burden and risks

On the visits at baseline and six months, extra blood (100 instead of 10mL) will be drawn during the standard phlebotomy and an endoscopic nasal polyp biopsy will be taken on one side and a nasal cyto-brush on the other side.

In patients with initial serum eosinophilia of >= 1.0 x 109/L, extra blood will also be drawn during the standard check-ups 4 and 12 weeks after treatment initiation (total 2 x 10 mL extra).

From 6 months on every 24 weeks up until and including 36 months: if during the standard check-up it is decided to prolong the interdose interval (conform daily practice), extra blood will be drawn during the standard phlebotomy (100mL instead of 10mL) and a nasendoscopic polyp tissue biopsy (if polyps are present) and cyto-brush is performed.

Risks of trial participation include:
- phlebotomy: possible increased discomfort
- biopsy: discomfort, minor bleeding
- cyto-brush: mild discomfort

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

bilateral CRSwNP (EPOS2020 criteria)
>= 18 years
indication for biological (EPOS2020 criteria) and starting treatment with dupilumab
(for EPOS 2020 criteria see reference in METC protocol)

Exclusion criteria

• age < 18 years
• pregnancy
• patient is not able to complete SNOT-22 questionnaire in NL or EN
• strong indication for surgical treatment (e.g.: mucoceles)
• systemic diseases affecting the nose (e.g.: GPA, EGPA, sarcoid, primary ciliary dyskinesia, cystic fibrosis)
• antrochoanal polyps (isolated benign polyps originating from the mucosa of the maxillary sinus with a distinctive small stalk)
• inverted papilloma and malignant polyps

• acute upper or lower respiratory tract infections within 2 weeks before the inclusion visit
• use of systemic corticosteroids within 4 weeks before the inclusion visit
• need of continuous systemic corticosteroid treatment for other disease than CRSwNP
• systemic diseases preventing participation in the study (all comorbidities that have a higher impact on quality of life than CRSwNP and/or making the patient at risk during the study period)
• other systemical medical treatments influencing disease or primary and secondary study outcome measurements such as (non-)selective immunosuppressants (e.g.: azathioprine, methotrexate), excluding co-treatment with other type-2 targeting
biologicals for indication of CRSwNP and/or Asthma.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-01-2021
Enrollment:	130
Type:	Actual

Ethics review

Approved WMO

Date:	16-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	26-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	NL75291.018.20