Early identification of progressive pulmonary fibrosis
Precision Medicine for more Oxygen - ILD extension

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1. Identify biomarkers and risk factors that associate with fibrosis progression or predict transformation into a rapid progressive (fibrosing) phenotype and acute exacerbations in IPF and FPF patients.2. Identify biomarkers and risk factors that...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON56954

Source
ToetsingOnline

Brief title
P4O2 ILD extension

Condition

- Respiratory disorders congenital
- Autoimmune disorders
- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
'Insterstitial Lung disease' 'lung fibrosis'

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Amsterdam UMC;AbbVie Inc.;and Boehringer Ingelheim Nederland contribute to the ILD cohort directly. Leids Universitair Medisch Centrum;Maastricht UMC+;Universiteit Maastricht;UMC Groningen;UMC Utrecht;Universiteit Utrecht;TNO;Aparito;Breathomix;Clear;Danone Nutricia Research;Fluidda;Ncardia;Novartis;Ortec Logiqcare;Philips;Proefdiervrij;Quantib-U;RespiQ;Roche;Smartfish;SODAQ;Thirona;TopMD;Lung Alliance Nederland (LAN) en de Longstichting Nederland (Longfonds)) en Health~Holland.,publiek-privaat consortium, deel van P4O2 consortium. Zie www.p4o2.org voor verdere informatie. Zie aanvullende informatie in brochure in K6. Er zitten op dit moment 27 organisaties in het consortium.

Intervention

Keyword: Biomarkers, Interstitial Lung Abnormalities, Interstitial Lung Disease, Progressive Pulmonary Fibrosis

Outcome measures

Primary outcome

- Pulmonary function test.

- Inflammatory and Fibrosis Extent assessed by High-resolution Computed

Tomography (HRCT) analyzed by using artificial intelligence software.

- Biomarkers related to pulmonary fibrosis will be measured in plasma and

serum.

- Peripheral Blood Mononuclear Cell (PBMC) populations in blood.

- Exhaled breath analysis including volatile organic compounds (VOCs) analysis

by gas chromatography-mass spectrometry (GC-MS).

Secondary outcome

- Disease-relevant questionnaires.

- Genomics, epigenomics, and transcriptome analysis in blood.

- Biomarkers related to pulmonary fibrosis will be measured in bronchoalveolar

lavage fluid (BALF), if it has been collected at clinical grounds or has been

performed in the subgroups.

- Lung tissue will be analyzed with histochemical techniques if available from clinical context e.g., diagnostic biopsies or lung explants.

- A subgroup of participants will be sampled using a ReCIVA breath analyzer from Owlstone and using a PExA instrument from PExA.

- External exposome analyses of thephysical/chemical environment.

- Biomarkers related to pulmonary fibrosis will be measured in a 24-hour urine collection.

- Metabolome analyses in urine and blood.

- Microbiome analyses in stool and nasal swabs.

Study description

Background summary

Interstitial Lung Disease (ILD) encompasses a heterogeneous group of lung disorders. Patients suffering from an ILD are at risk for the development of pulmonary fibrosis (PF). This subgroup as a whole is called fibrotic ILD (fILD) patients. PF is characterized by excessive deposition of extracellular matrix (ECM) by activated fibroblasts in the lungs, leading to irreversible pulmonary function decline, respiratory failure, and eventually death in patients.

Idiopathic Pulmonary fibrosis (IPF) is the most frequent fibrotic ILD with the worst prognosis compared to other ILDs. IPF and Familial Pulmonary Fibrosis (FPF) exhibit comparable clinical trajectories and are treated similarly, but treatment options are limited. Both IPF and FPF patients are at risk for the development of acute exacerbations, which are episodes of sudden and severe progression of the disease that appear to be irreversible (lost lung function will not be restored). In arm 1 of this study, we aim to identify biomarkers and risk factors that associate with fibrosis progression or can predict the transformation into a rapidly progressive (fibrosing) phenotype and acute exacerbations in IPF and FPF patients.

The development of progressive pulmonary fibrosis (PPF) is also frequently seen in other forms of ILD, indicating common underlying mechanisms. Currently, the

definition of PPF is based on changes in clinical parameters over time (see Table 1), meaning that at the time of diagnosis, loss of pulmonary function due to irreversible fibrosis has already occurred. Consequently, the optimal timing for initiating treatment is a subject of ongoing debate, emphasizing the critical importance of early detection of PPF-ILD. Arm 2 of this study aims to identify biomarkers and risk factors that can predict the development of a PPF phenotype among various forms of fILDs, enabling early detection and intervention.

Moreover, to get a better understanding of the development of clinically significant (progressive) fILD, we will investigate interstitial lung abnormalities (ILAs). ILAs are considered radiologic abnormalities that are characteristic of early-stage ILDs and can be detected without clinical suspicion of an ILD. It is unknown which ILAs progress to clinically relevant ILDs with fibrosis and at what rate. Arm 3 of this study aims to identify biomarkers and risk factors for the development of a clinically relevant fILD in ILA patients. The results from this part of the study will contribute to the development of monitoring strategies for ILA patients and provide further insights into disease development.

Study objective

1. Identify biomarkers and risk factors that associate with fibrosis progression or predict transformation into a rapid progressive (fibrosing) phenotype and acute exacerbations in IPF and FPF patients.
2. Identify biomarkers and risk factors that predict the development of a PPF phenotype among different forms of fILD.
3. Define biomarkers and risk factors for the development of clinically significant fILD among ILA patients.
4. Identify biomarkers and define risk factors that might predict treatment response within fILD (secondary objective).

Study design

Non-Interventional Prospective Observational Cohort Study

Study burden and risks

Participants will visit the clinic multiple times for the collection of clinical data and samples. The visits of patients in arm 1 and 2 align with the regular diagnostic path and follow-up process outlined in the ILD/IPF Care Path Protocol of Amsterdam UMC (referred to as Zorgpad in Dutch), which can be found in Appendix 15.1. No additional study visits are requested for these participants. Pulmonary function tests and high-resolution Chest Tomography (HRCT) scans obtained from routing clinical care will be used and will not be obtained as part of the study protocol. Also immunological BALF and lung tissue

biopsies will only be collected during procedures that are necessary for clinical care purposes. For the participants in arm 1 and 2 only minimally invasive measurements will be obtained during routine clinical visits.

ILA participants of arm 3 will be recruited from different routes, e.g. the Dutch thoracic radiology network, from the NVvR (in Dutch: Nederlandse Vereniging voor Radiologie (NVvR);, Dutch Society of Radiologists), P4O2 PARASOL cohort and the national lung cancer screening protocols. ILA individuals that are identified, will be asked to participate in the study protocol and to align with the study visits as described. Even though these individuals are at risk for the development of a symptomatic ILD, currently there is no indication for clinical follow-up of these patients. The study visits, including pulmonary function tests and yearly HRCT are an additional burden compared to patients in arm 1 and 2, but may also show a clinical benefit as progression to a clinically relevant ILD will be observed earlier. Moreover, this study may provide valuable data that may provide clues for important clinical follow-up of ILA individuals in the future. All measurements and data collections are similar to the participants in arm 1 and 2 which also allows for proper comparison between the different arms.

Additionally, extra measurements will be performed during one of the following events: 1. signs of rapid progression outside the fixed time points; 2. treatment switch; 3. lung transplantation; 4. acute exacerbation; or 5. development of pulmonary hypertension. Again, this corresponds with extra visits needed for standard clinical care during these events, allowing for easy integration of the additional study measurements. Standard patient care will not be interfered with or compromised at any time, and no (therapeutic) interventions will be performed in the study protocol.

Next to these events we will ask two subgroups, 30 participants in arm 2 and 30 participants in arm 3, to undergo (an additional) bronchoscopy with immunological BAL for biomarker measurements and immune cell analysis in BALF. The 30 participants in arm 2 will be selected if a bronchoscopy with immunological BAL was performed at baseline also. For the participants in arm 3 we will perform this procedure in the first year after recruitment. This procedure is frequently performed in pulmonary practice and carries a small risk of potential complications, including fever, bleeding, respiratory depression, or pneumothorax, which occurs in less than 1% of the cases.

For all participants, the specific data collected at each time point are described in detail in Section 3 of this protocol. In short, upon signing the informed consent form, baseline measurements (T0) will be performed, including the collection of clinical data, the completion of questionnaires, blood and urine sample collection, pulmonary function tests, HRCT scans, exhaled breath analysis, stool sample collection, and nasal brush sampling. Exposome samples, which capture the air contents of the participants* living environments, will be collected during two separate visits at the participants* homes,

corresponding to different seasons (spring and autumn). Whenever possible, procedures that are already performed as part of routine clinical care, like HRCT scans, pulmonary function tests and blood sampling, will be used to minimize any additional burden on participants.

Pulmonary function tests and exhaled breath analysis have little to no burden, although some participants may experience dizziness after the tests. Additional blood samples needed for biomarker analysis usually do not pose an extra burden, as these patients are typically monitored for clinical or pharmacological parameters. In some cases, an additional vena puncture has to be performed, but this procedure is generally well-tolerated by participants. Vena punctures are also performed for clinical care and will be combined with protocol vena punctures, with each puncture limited to 75ml per time point. To assess quality of life, disease-relevant questionnaires will be obtained at baseline and at 6, 12, 24, 36, 48, and 60 months. The burden of the nasal brushes is also mild, although participants may find the procedure slightly uncomfortable for a very short duration. Other sample collections, such as urine, stool, and exposome sampling, require minimal effort and time from the participant.

HRCT scans obtained in arm 3 will result in increased radiation exposure of the participants as these or not part of standard clinical care. Radiation exposure of an HRCT scan is however very low (5.5mSv for in- and expiration scan) which is slightly more than two times the average annual radiation exposure per individual in the Netherlands which is 2.6mSv (Central Organization For Radioactive Waste [COVRA]). Clinical follow-up of ILA participants may show clinical benefit in a subgroup of these patients leading to earlier detection and intervention of a clinical relevant ILD.

Contacts

Public
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

To be eligible to participate in this study, subjects must meet all of the following criteria:

Arm 1
- IPF/FPF diagnosis (non-stratified) within 1 year prior to screening, based on the guidelines set by ATS/ERS/JRS/ALAT (Raghu et al., 2022)(Zhang & Newton, 2021). A chest HRCT should have been performed within 12 months prior to screening, meeting the minimum requirements for IPF diagnosis by multidisciplinary consultation consensus in the ILD-expertise center based on HRCT or HRCT and lung biopsy if available. If no HRCT is available prior to screening, it can be performed at the screening;
- Meeting all of the following criteria during the screening period:
1. FVC >=45% predicted for normal.
2. FEV1/FVC >=0.7.
3. DLco corrected for Hb >=40% predicted of normal.
- Able to provide written informed consent as approved by the independent ethics committee;
- Able to undergo a CT scan and perform pulmonary function testing;
- Age >18 years and <80 years;
- Understanding the Dutch or English language.

Arm 2
- Fibrotic ILD diagnosis based on the ATS/ERS/JRS/ALAT guidelines, classified into one of the four defined subgroups (chronic/fibrotic HP, iNSIP, CTD-ILD, or unclassifiable ILD; non-stratified)(Raghu et al., 2020; Ryerson et al., 2013; Shao et al., 2021; Travis et al., 2013). A chest HRCT should have been performed within 12 months prior to screening, meeting the minimum requirements for fILD diagnosis by multidisciplinary consultation consensus in the

ILD-expertise center based on HRCT or HRCT, serologic markers (e.g., antibodies, biomarkers), and/or BALF/ung biopsy (if available). If no HRCT is available prior to screening, it can be performed at the screening;
- Minimum of 10% involvement of the lung parenchyma on HRCT and signs of fibrosis, defined as traction bronchiectasis/bronchiolectasis, lobar volume loss, and/or honeycombing (investigator-determined);
- Meeting all of the following criteria during the screening period:
1. FVC >=45% predicted for normal.
2. FEV1/FVC >=0.7.
3. DLco corrected for Hb >=40% predicted of normal.
- Able to provide written informed consent as approved by the independent ethics committee;
- Able to undergo a CT scan and perform pulmonary function testing;
- Age >18 years and <80 years;
- Understanding the Dutch or English language.

Criteria BAL candidates Arm 2/ f-ILD-group:
- BAL at diagnosis available;
- Progression after 1 year of follow-up;
- No contra-indications for performing BAL e.g. allergies;
- Performance of BAL is low-risk estimated by clinical physician.

Arm 3
- ILA is defined according to the current guidelines set by the Fleischner Society (Hatabu et al., 2020). A chest HRCT should have been performed within 12 months prior to screening, meeting the minimum requirements for ILA diagnosis by multidisciplinary consultation consensus in the ILD-expertise center based on HRCT only or HRCT and lung biopsy if available.
- Meeting all of the following criteria during the screening period:
1. FVC >=45% predicted for normal.
2. FEV1/FVC >=0.7.
3. DLco corrected for Hb >=40% predicted of normal.
- Able to provide written informed consent as approved by the independent ethics committee;
- Able to undergo a CT scan and perform pulmonary function testing;
- Age >18 years and <80 years;
- Understanding the Dutch or English language.

Criteria BAL candidates Arm 3/ILA-group:
- BAL at diagnosis possible;
- No contra-indications for performing BAL e.g., allergies;
- Performance of BAL is low-risk estimated by clinical physician.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

Arm 1
- Combined pulmonary fibrosis and emphysema (CPFE) is defined by the coexistence of pulmonary fibrosis and emphysema, as described in the latest paper by Cottin et al. (2022). To meet the criteria for CPFE on high-resolution computed tomography (HRCT), patients must exhibit: emphysema of any subtype, characterized by well-demarcated areas of low attenuation delimited by a very thin wall (<1 mm) or no wall, involving at least 5% of the total lung volume and lung fibrosis of any subtype (Cottin et al., 2022).
- Chronic obstructive lung disease (COPD) with an FEV1/FVC <70%;
- Uncontrolled severe asthma;
- Active malignancy, except for squamous cell carcinoma of the skin, low-risk breast cancer, and low-risk prostate cancer;
- Pregnancy or lactating.

Arm 2
- Combined pulmonary fibrosis and emphysema (CPFE) is defined by the coexistence of pulmonary fibrosis and emphysema, as described in the latest paper by Cottin et al. (2022). To meet the criteria for CPFE on high-resolution computed tomography (HRCT), patients must exhibit: emphysema of any subtype, characterized by well-demarcated areas of low attenuation delimited by a very thin wall (<1 mm) or no wall, involving at least 5% of the total lung volume and lung fibrosis of any subtype (Cottin et al., 2022).
- Chronic obstructive lung disease (COPD) with an FEV1/FVC <70%;
- Uncontrolled severe asthma;
- Active malignancy, except for squamous cell carcinoma of the skin, low-risk breast cancer, and low-risk prostate cancer;
- Pregnancy or lactating.

Arm 3
- Combined pulmonary fibrosis and emphysema (CPFE) is defined by the coexistence of pulmonary fibrosis and emphysema, as described in the latest paper by Cottin et al. (2022). To meet the criteria for CPFE on high-resolution computed tomography (HRCT), patients must exhibit: emphysema of any subtype, characterized by well-demarcated areas of low attenuation delimited by a very thin wall (<1 mm) or no wall, involving at least 5% of the total lung volume and lung fibrosis of any subtype (Cottin et al., 2022).
- Chronic obstructive lung disease (COPD) with an FEV1/FVC <70%;
- Uncontrolled severe asthma;
- Active malignancy, except for squamous cell carcinoma of the skin, low-risk breast cancer, and low-risk prostate cancer;
- Medical history with pulmonary related auto-immune diseases;
- Family history with familial fibrosis (FPF);
- Pregnancy or lactating.

Additional exclusion criteria for the subgroups (n=60):
- In a subgroup of participants from arm 2 (n=30) and arm 3 (n=30), who undergo an (additional) immunological bronchoalveolar lavage (iBAL) procedure, participants with absolute contra-indications to undergo bronchoscopy with iBAL will be excluded. Absolute-contra-indications are allergies to lidocaine, midazolam, or xylometazoline, acute myocardial ischemia, and hemodynamic instability in accordance with the protocol Bronchoscopy with immunological BAL (in Dutch: Bronchoscopie met immunologische B.A.L) of the Amsterdam UMC (added in Appendix 15.2).

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-11-2024
Enrollment:	450
Type:	Actual

Ethics review

Approved WMO

Date:	31-07-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL84006.018.23