ADDED VALUE OF [^{18}F]-FDG-PET-CT IN THE DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS IN NEUTROPENIC PATIENTS

Protocol ID	NL36621
Short title	Added value of FDG-PET-CT in invasive fungal infections in neutropenic patients
Version	1
Date	01-05-2011
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PROTOCOL SIGNATURE SHEET

Name	Signature	Date
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SUMMARY

Rationale: Invasive fungal infections (IFIs) can be life threatening, especially in prolonged neutropenic patients. The overall mortality in this group has decreased from 60-80% in the past to 30-40% today because of better diagnostics and antifungals. It is essential to diagnose IFIs and start the right treatment as soon as possible to increase survival rates of the patients. Nowadays, HR-CT as imaging technique and galactomannan (GM)-test (Elisa) in blood and fluid (obtained by broncho-alveolar lavage) are together considered the "gold standard" for diagnosing IFIs, but both techniques have their limitations and provide probable diagnosis at best. It is therefore of invaluable importance to have another non-invasive test which can provide a higher sensitivity and specificity for diagnosing these IFIs. ^{18}F-FDG-PET, and even better the combined PET-CT scan (which correlates anatomic with pathophysiologic imaging) might be this important non-invasive imaging technique with better characteristics to early diagnose IFIs.

Objective: The primary objective of this pilot study is to compare FDG-PET-CT with HR-CT alone and to HR-CT and galactomannan test together for early diagnosing IFIs in neutropenic patients.

Study population: Twelve hematologic patients (age > 18 years with neutropenia and prolonged fever after 72 hours of broad-spectrum antibiotics) will be included in this study. Six of 12 patients will have positive signs (one nodule or more noduli) on the HR-CT for IFI and a positive galactomannan-test, therefore having a probable IFI per definition. Furthermore, six out of 12 patients will have positive signs on HR-CT scan without a positive GM test, therefore having a possible IFI.

Study design: All twelve patients will undergo, within 48 hours of the HR-CT, an FDG-PET-CT scan (low dose CT) on the mCT (Siemens) camera at the Department of Nuclear Medicine and Molecular Imaging. The FDG-PET-CT will be evaluated qualitatively and quantitatively by calculation of the maximal Standardized Uptake Value (SUVmax). These quantitative parameters will be correlated with the results of the galactomannan-tests. Treatment schedule will be similar as normal treatment procedures, i.e. treatment regimen will not depend on the results of the FDG-PET-CT. We hope to find that FDG-PET-CT is able to localize IFI with more accuracy and give us pathognomic signs in this group of patients for having an IFI. This pilot study can form the basis for larger patient studies to see if FDG-PET-CT is able to detect IFI with greater sensitivity and specificity and eventually replace the invasive galactomannan-test by broncho-alveolar lavage.

1. INTRODUCTION AND RATIONALE

Invasive fungal infection (IFI) can be life threatening, especially in neutropenic patients. One of the most notorious pathogens causing these infections is a mold called Aspergillus. Diagnosing IFI in neutropenic patients is difficult. A lung biopsy as golden standard for proven invasive aspergillosis is often not possible due to thrombocytopenia and due to a difficult procedure to reach non-peripheral localized lung lesions. Furthermore, there is a chance of pneumothorax after this CT-guided biopsy has been performed. The benefit of a broncho-alveolar lavage (BAL) is also questionable when peripheral localized lung lesions are involved because the BAL fluid will not reach these lesions. On the other hand it may be helpful to exclude other causes of neutropenic fever, like PCP or viral pathogens. Nowadays High Resolution CT-scan (HR-CT) of the thorax and a galactomannan-test (galactomannan is a component of the cell wall of the aspergillus) in serum and fluid acquired by BAL are the next best ("silver') standard procedures for diagnosing IFIs.

However, galactomannan (GM) has a low sensitivity for fungal infections in general; it is only suitable for infections caused by Aspergillus, but other fungi, such as mucor, are not detected with this test. The sensitivity and specificity of GM detection in BAL fluid was 88 and 87%, respectively. However, the sensitivity of serum GM was only 42%. [1] Pathognomonic signs on the HR-CT scan are the *halo sign* (a zone of low density surrounding the real lesions), the *air crescent sign* (lung cavities filled with air and a round radio opaque mass, which can only be seen in advanced and prolonged IFIs after recovering of neutrophils in the blood and therefore not in an early stage of IFI), and nodular lesions. In the clinical setting, HR-CT is often inconclusive because the afore mentioned signs can be aspecific, e.g. the halo-sign can also appear in other infectious and non-infectious diseases, such as neoplastic and inflammatory conditions, or even disappear within a few days. [2] Another disadvantage of the HR-CT of the thorax is that non-infectious pathology and lesions outside the lungs cannot be visualized.

Treatment of IFIs remains, even when recognized early, problematic because the response of a patient on antifungal treatment depends on the depth and the duration of this immunosuppressed (mostly granulocytopenic) condition. Therefore, it is essential to diagnose IFIs and start the right treatment as soon as possible to increase survival rates of the patients. It is therefore of invaluable importance to have an imaging method for diagnosing these IFIs that has a higher sensitivity and specificity than the HR-CT with and without the galactomannan-test. Therefore, we want to study the added value of FDG-PET-CT compared to the HR-CT with and without a positive galactomannan-test.

^{18}F-FDG-PET, and even better the combined PET-CT scan (which correlates anatomic with pathophysiologic imaging), will maybe be this important non-invasive imaging technique to early diagnose IFIs.

FDG-PET is used already for many years in daily practice in many infectious diseases. This technique is also used incidentally in various fungal infections, such as aspergillosis, candidiasis, histoplasmosis, coccidioidomycosis, cryptococcosis and Pneumocystis jiroveci. [3-9] However, systematical use of FDG-PET in patients suspected of IFIs is virtually absent.

Sometimes these infections were found by coincidence in patients that were scanned for other reasons such as (recurrent) malignancy.

The largest study was published by Chamilos et al. who reported their own experiences in 13 patients with the results of nine patients in literature. Most patients had an underlying malignancy (73%), primarily of haematological origin (55%) and 7 were allogeneic haematopoietic stem cell transplants recipients. Importantly to notice, the vast majority of these immunocompromised patients (82%) were non-neutropenic at the time of diagnosis of IFI. They found that FDG-PET frequently found occult lesions not found with other imaging techniques (3 out of 16 patients with available follow FDG-PET imaging studies), and that the results helped to determine treatment length in 8 of these 16 patients. Overall, FDG-PET was deemed to be helpful in 10 out of the 16 (60%) eligible patients. [10] However, it remains unclear whether these results also apply for neutropenic patients.

For the combined PET-CT almost no studies were found in literature for the indication ‘fungal infections in neutropenic patients’. Three reports of in total five patients showed that FDG-PET-CT is effective in diagnosing IFIs. [11-13]

In this study we will include patients who have a possible or probable IFI, which means positive signs on the HR-CT for IFI and without or with a positive galactomannan-test in blood and/or BAL. To get final proof of IFI a biopsy would be necessary, however as explained before, this is often not possible due to the thrombocytopenic state of the patients. We hope to find pathognomic signs on the FDG-PET-CT that probably can replace the now needed invasive galactomannan-test by broncho-alveolar lavage, which is a considerable burden for the patient and not performable when the patient is clearly dyspnoic.

2. OBJECTIVES

Primary Objective:

To evaluate if FDG-PET-CT has added value compared to HR-CT and galactomannan-test, nowadays the silver (or surrogate gold) standard diagnostic techniques for early diagnosing IFIs in neutropenic patients. To evaluate this added value we have the following questions:

- Has FDG-PET-CT additional value as imaging modality compared to the HR-CT thorax? Are their specific imaging characteristics found on FDG-PET-CT in relation to the 3 different described lesions found by HR-CT? Can FDG-PET-CT also provide information about the extension of the known lesions, i.e. is the halo sign on HR-CT involved in the infectious process or is it a sign of decreased perfusion due to infarction?
- Can FDG-PET-CT detect enlarged and/or positive lymph nodes and what is the meaning of these lymph nodes in relation to prognosis or GM detection?
- Is FDG-PET-CT able to find additional infectious lesions that are not visible on HR-CT of the thorax? Can FDG-PET-CT detect smaller lesions than HR-CT by its metabolic positivity and is there a relation between the total amount of metabolic positivity of lesions (mean SUV times area of positivity) and galactomannan positivity, which is a parameter of activity and/or invasiveness of aspergillosis?
- Is FDG-PET-CT able to find additional infectious lesions that are not visible on HR-CT of the thorax because they are found outside the thorax? Sometimes IFI are found in the sinussen or gut or brain or combinations of these localisations.

3. STUDY DESIGN

This study is a pilot study in a total of 12 hematologic patients with prolonged neutropenia and fever, positive signs for IFI on the HR-CT with or without a positive galactomannan test, therefore having a probable (N=6) or possible (N=6) IFI by definition. Within 48 hours of the HR-CT scan these patients will undergo an additional FDG-PET-CT scan (low dose CT) on the mCT (Siemens) camera in the Department of Nuclear Medicine and Molecular Imaging. The FDG-PET-CT will be evaluated qualitatively and quantitatively by calculation of the maximal Standardized Uptake Value (SUVmax).

4. STUDY POPULATION

4.1 Population

Twelve patients with prolonged neutropenia and fever, positive signs for IFI on the HR-CT and a positive (N=6) or negative (N=6) galactomannan-test, therefore having a probable or possible IFI, will be recruited from the Department of Internal Medicine, Division of Haematology. Because these patients are routinely seen in this Department we expect no problem with recruiting these patients.

4.2 Inclusion criteria

Adult patients (age > 18 years) with a hematologic disease who probably or possibly have an IFI. That means:

- Prolonged (or expected prolonged) neutropenia (leukocyte count < $1{,}0x10^9$ or granulocyte count < $0{,}5x10^9$, or leukocyte count < $1{,}5x10^9$ or granulocyte count < $1{,}0x10^9$ and decreasing due to chemotherapy), and
- Axillary temperature ≥ 38, 5°C, not reacting on treatment with wide-spectrum antibacterial drugs for 72 hours, and
- A positive HR-CT scan, suspect for an IFI and
    - A positive galactomannan-test in serum or fluid acquired by BAL, or positive in both materials (N=6)
    - A negative galactomannan-test GM in both serum and BAL fluid (N=6)

4.3 Exclusion criteria

- Patients with age < 18 years
- Female patients who are pregnant
- Patients with claustrophobia or other reasons that make the scanning impossible, such as unable to lie still, need of oxygen, and so on.
- Patients who are hemodynamically instable
- (Pre)terminal patients for which the investigation is too burdensome
- Patients who may clinically not be able to undergo the study
- Patients without prolonged or expected prolonged immunocompromised condition (less than 14 days)
- Patients without positive signs of IFI on HR-CT

4.4 Sample size calculation

This study is a pilot study in twelve hematologic patients who have a probable or possible IFI. Because most of these patients will actually have an IFI, we think these are enough patients to study the added value of FDG-PET-CT in this group of patients to conclude if larger patient studies are wanted.

5. TREATMENT OF SUBJECTS

This chapter is not applicable in this study.

5.1 Investigational product/treatment

This is not applicable in this study.

5.2 Use of co-intervention (if applicable)

This is not applicable in this study.

5.3 Escape medication (if applicable)

This is not applicable in this study.

6. INVESTIGATIONAL MEDICINAL PRODUCT

The Investigational Medical Product Dossier (IMPD) of the used PET tracer ^{18}F-FDG can be read in the attached document.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

This is a pilot study. After 12 patients the study will be ended and evaluated.

7.1.2 Secondary study parameters/endpoints (if applicable)

This is not applicable in this study.

7.1.3 Other study parameters (if applicable)

This is not applicable in this study.

7.2 Randomisation, blinding and treatment allocation

This is not applicable in this study.

7.3 Study procedures

When the (conventional) diagnostic tools are performed and a patient probably or possibly has an invasive fungal infection, FDG-PET-CT (low dose CT) scan will be planned as soon as possible, but within 48 hours of the HR-CT scan on the mCT camera (Siemens).
When the (conventional) diagnostic tools are suspicious for an IFI antifungal treatment will be started, independent of the FDG-PET-CT results. Treatment will be continued conform normal treatment procedures, i.e. treatment regime will not depend on the results of the FDG-PET-CT.

Patient recruitment:
Informed consent will be obtained by Dr. Span or Dr. Daenen from the Department of Internal Medicine, Division of Hematology. When the patient decides to participate he/she will be asked to sign the informed consent form. The normal diagnostic and therapy protocols will not be changed; other imaging studies will not be delayed. Patients can contact an independent doctor (Dr. R.H.J.A. Slart) in case they feel the need to receive information from a doctor who is not involved in the study.

Preparation and labelling of [^{18}F]-FDG:
^{18}F-FDG will be prepared according to the standard protocol at the department of Nuclear Medicine and Molecular Imaging as is described in the IMPD.

[^{18}F]-FDG-PET-CT protocol:
A routine whole body PET (that means from head till halfway the upper legs) will be performed 60 minutes after the intravenous injection of 3-5 MBq per kilogram [^{18}F]-FDG conform normal administrated activity in patients. A low dose CT will be

performed simultaneously for attenuation correction and for anatomic correlation with the PET images. The total scanning time will be around 25 minutes.

Evaluation of the FDG-PET-CT scan:
The FDG-PET-CT will be evaluated qualitatively and quantitatively by an experienced nuclear medicine physician, with special attention to finding lesions outside the thorax, the extension of the lesions found compared to the HR-CT lesions and to the intensity of the uptake of FDG by calculating the SUVmax. These quantitative results will be compared to the results of the galactomannan-tests.

Radiation dose considerations:
Use of positron emitting radionuclides means exposure to ionizing radiation. Because of the potential hazard of radiation, guidelines for the exposure of healthy volunteers and patients are specified in “Besluit Stralingsbescherming (BS 2000), artikel 60, Staatsblad 2001, 397”, according to the guidelines of the International Commission on Radiological Protection.

The radiation exposure of one FDG-PET-CT (low dose CT) is approximately 9.1 mSv (7.6 mSv for FDG-PET and 1.5 mSv for low dose CT). This complies with category IIb, IRCP 62.
The radiation dose calculation is approved by our local clinical physicist dr. J.R. de Jong.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

A total of twelve patients is required in this pilot study. When a patient withdraws another patient will be recruited.

7.6 Follow-up of subjects withdrawn from treatment

This is not applicable in this study.

7.7 Premature termination of the study

This is not applicable in this study.

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the diagnostic procedure]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

Due to the nature of the present investigation, no procedure-related adverse events or SAEs are expected to occur, but IFI itself or the underlying disease may cause severe complications.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

This is not applicable in this study.

8.2.2 Annual safety report

This is not applicable in this study.

8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.4 Data Safety Monitoring Board (DSMB)

This is not applicable in this study.

9. STATISTICAL ANALYSIS

Statistical analysis is not necessary in this pilot study. The lesions found on the FDG-PET-CT will be described in the report and compared to other diagnostic techniques. The FDG-PET-CT scan will be evaluated qualitatively (by visual evaluation of the uptake) and quantitatively (by calculating the SUVmax). The calculated SUVmax will be compared to the results of the galactomannan-tests. The aim of this study is to see if FDG-PET-CT is able to localize the IFI and if pathognomic signs for IFIs can be found.
We expect positive signs on the FDG-PET scan in all patients with probable fungal infections. Of the six patients with possible infections we expect at least 2 or 3 to have positive signs on FDG-PET scan. If we can find additional information (positive lymph nodes, lesions in other part of the body) we can not predict.
When there is added value of the FDG-PET-CT we will arrange a larger patient study for which statistical analysis is necessary. Power calculation is not applicable in this study because the aim of this study is to get data to plan a larger clinical study with the appropriate power calculation. These data will serve to calculate the power analysis for a subsequent clinical study.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

Patient recruitment and informed consent will be obtained by Dr. Span and Dr. Daenen from the Department of Internal Medicine, Division of Haematology. When informed consent is signed the Department of Nuclear Medicine and Molecular Imaging will schedule the FDG-PET-CT within 48 hours from the HR-CT and inform the patient about the scan procedure. Patients may withdraw from this study at any time, without prejudice to further treatment. The patient information letter and informed consent form are attached as separate documents.

10.3 Objection by minors or incapacitated subjects (if applicable)

This is not applicable in this study.

10.4 Benefits and risks assessment, group relatedness

The patients who are participating in this study will not have benefits from this scan in the way that their treatment decisions will not depend on the results of FDG-PET-CT scans. Diagnostic and treatment procedures will be followed as normal. We hope this pilot study will reveal that FDG-PET-CT is a valuable tool for the diagnosis and evaluation of treatment in this patient group and that in the future this imaging tool can be used as the imaging method of choice.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;

2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

This is not applicable in this study.

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Medical history and data from this study will be used for scientific purposes. Medical history data include: history of disease, diagnostic and therapeutic data, other scans performed, results of HR-CT, BAL and galactomannan tests and laboratory parameters. Study data include: data of the FDG-PET-CT scan. Data of the patients will be coded in our research database. Only the project leader and the principal investigators of the study will have access to the patient data. Names of patients will not be visible in scientific publications. Data will be stored after finishing the data analysis. Digital data are protected by our local hospital information system. This will also protect the data to dissemination outside the hospital. No reports of the patients of our protocol will appear in the hospital system.

11.2 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety, or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included, and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.4 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.
In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.5 Public disclosure and publication policy

The results of this study will be published in medical scientific journal(s) by the coordinating investigator (A.W.J.M. Glaudemans) and the principal investigators. There is no arrangement made concerning the public disclosure and publication of the research data.

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