Study Plan

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Study Title

A Multicenter Analysis of Isavuconazole for Treatment of Probable/Proven Mucormycosis and Invasive Aspergillosis

Running Title

Isavuconazole-Registry

Summary

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Rationale	To evaluate the role and impact of isavuconazole for inpatient treatment and clinical management of probable/proven invasive aspergillosis and mucormycosis in the hematological real-life setting.
Primary Objective(s)	Clinical effectiveness and potential health-economic benefits of isavuconazole in treatment of invasive aspergillosis/mucormycosis compared to patients who received liposomal amphotericin B and/or voriconazole.
Study Design	This is an observational cohort study using a 1:1 ratio including 150 patients in the isavuconazole group (case group) and 150 patients in a matched control group from up to 10 German tertiary care centers with broad experience in treatment of hematological diseases. Data collection will be performed retrospectively after a regular discharge or death. Only data from standard of care treatment will be collected (secondary data use) and all data will be documented into a web-based eCRF by using the www.ClinicalSurveys.net platform.
Study Population	Hematological patients with probable/proven invasive aspergillosis and/or mucormycosis defined by the EORTC/MSG criteria.
Study Duration	19 months including data documentation, statistical analysis, and final report.
Exposure and Outcome	Clinical effectiveness and health-economic impact of isavuconazole in treatment of probable/proven invasive aspergillosis and/or mucormycosis.
Statistical Methods	Sociodemographic and clinical differences between the case group and the control group will be compared using Mann-Whitney-U test or t-test, as applicable. A binary logistic regression analysis will be performed to identify independent factors associated with treatment success and overall outcome. We will use Kaplan Meyer and Cox-regression model to analyze the impact of covariates on survival until the end of inpatient treatment. Health-economic analyses, including direct healthcare treatment costs, will be performed by using Welch´s bootstrapped t-test. Furthermore, a multivariate generalized linear model (GLM) with gamma distribution and log-link will be applied to analyze variables influencing overall direct treatment costs.
Limitation(s)	In observational studies, the treatment selection can be influenced by subjects' baseline characteristics. However, we will perform an adjusted analysis to minimize bias due to subjects' baseline characteristics.

Background and Rationale

Invasive fungal diseases (IFDs), such as invasive mucormycosis and aspergillosis, are life-threatening infections with mortality rates up to 75% [1-3]. One major reason of fatal outcome is the considerable low rate of response to first-line treatment (e.g. due to nephrotoxicity), mostly resulting in salvage therapy with poor outcome [4-6]. The incidence of rare fungal infections, also well known for high morbidity and mortality rates, increased during the last years [7, 8]. Next to the clinical burden of IFDs, recently published studies demonstrated high treatment costs [9-11].

Additionally, the increasing prevalence of immunocompromised high-risk patients and the overall increase of IFDs demonstrate the urgent need to develop new treatment strategies. Isavuconazole, a triazole antifungal agent, has a broad spectrum of activity against many pathogenic fungi and a low rate of side effects. It was approved in 2015 by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of invasive mucormycosis and invasive aspergillosis, after clinical trials evaluated the safety and efficacy compared to voriconazole and voriconazole/caspofungin [12].

To our knowledge, real-life data outside the environment of clinical trials regarding a clinically and economically sound strategy of isavuconazole in treatment of invasive mucormycosis and aspergillosis does not exist. To date, only a few studies exist modeling cost-effectiveness based on the phase III SECURE and VITAL trial [13-15].

Study Project

We propose to perform a retrospective, multicenter analysis of hematological patients with probable/proven mucormycosis and aspergillosis treated in German tertiary care centers. The primary study aim will be to analyze potential clinical and economical benefits for the German healthcare system by using isavuconazole for the above mentioned indications.

The study will be performed in a matched case/control design of patients who received isavuconazole (case group) vs. liposomal amphotericin B or voriconazole (control group) by using our www.ClinicalSurveys.net platform. This platform, which was set up by researchers of the University Hospital of Cologne (UHC) in corporation with the Globalpark AG (now Queckback GmbH, Cologne, Germany), enables an optimal performance in epidemiological, non-interventional, and health economic trials [16, 17, 10, 18].

Only patients who received first-line treatment for IFDs will be included. To ensure granular data documentation, data items of interest will be patient characteristics, risk factors, clinical signs and symptoms, sites of infection, diagnostic procedures (e.g. imaging, microbiology), antifungal treatment (dose, duration, and administration route), co-medication (e.g. other antiinfective agents) length of stay (including different wards), and outcome. With respect to the health-economic evaluation, a micro-costing approach based on the German Diagnosis Related Groups (G-DRG) systematic will performed to guarantee the most comprehensive view on direct treatment costs.

Study Design

The study will be designed based on the following information/sources:

- Inpatient chart review of 300 patients from up to 10 German tertiary care centers (information based on our feasibility analysis with corresponding partners)
- All data items will be documented into an eCRF accessible via www.ClinicalSurveys.net
- All German tertiary care centers with hematology/oncology units are invited to participate
- If needed, announcement of the study will be performed by using the platform of the Infectious Disease Working Party of the German Society of Hematology and Medical Oncology (AGIHO/DGHO)
- Case/control design in a 1:1 ratio (150 patients each in the case and control group)
- Matching of control patients from the same participating center will be performed by using the following criteria:
    - Age +- 10 years
    - Gender
    - Underlying disease
    - Underlying conditions (e.g. chemotherapy cycle)
    - Type and grade of fungal infection
    - If treated on an ICU: APACHE score
        - If the patient included into the case group underwent an allogeneic stem cell transplantation (alloSCT) or an autologous stem cell transplantation (autoSCT) during the inpatient stay, the control patient must also received a alloSCT or autoSCT during the inpatient stay. Patients are then matched according to the grade of graft versus host disease (GvHD):No GvHD
        - Acute GvHD grade 1 or 2
        - Acute GvHD grade 3 or 4
        - Chronic GvHD

Data Documentation

Data documentation will be performed strictly anonymous. All data will be retrospectively documented following hospital discharge (regular or death) into an eCRF as mentioned above. Documentation can be performed by the participating centers or delegated to our trained personnel to speed up the process and reduce workload at the participating center. Data monitoring, query management, and analysis of data will be performed by the academic researchers of the UHC.

Patient Population

- Inpatient stay in a hematology/oncology department between 01/2016 – 05/2021
- Hematological or oncological underlying disease
- Male or female 18 years of age or older
- Evidence of probable/proven aspergillosis or mucormycosis based on revised EORTC/MSG criteria [19]

Variables

The eCRF will ensure the following variables:

- Patient characteristics (age, gender, ethnicity)
- DRG/OPS codes
- Risk factors for IFD
- Type and grade of IFD (probable/proven)
- Clinical symptoms of IFD
- Surgical interventions due to IFD
- Duration of all hospital stays on different wards (general ward, intermediate care, intensive care unit)
- Antifungal treatment (duration, dose, administration route)
- Other concomitant medication and interacting drugs (e.g. antibacterials, antifungals, antivirals, conditioning therapy)
- Therapeutic drug management (TDM)
- Adverse events (AE) (in relationship with isavuconazole)
- Microbiological and clinical diagnostic (e.g. CT scan)
- Resistance testing of fungal pathogens
- Further direct treatment cost factors (e.g. diagnostic measures, laboratory tests, antiinfective treatment, mechanical ventilation, rehospitalisation)
- Other co-infections
- Outcome of antifungal treatment (failure, success, switch to another agent)
- Overall outcome (regular discharge, death)

Hypothesis

- Isavuconazole will be effective in treating IFDs
- Beneficial role of isavuconazole with respect to pharmacokinetics, safety, and tolerability
- Sufficient serum levels of isavuconazole will be reached
- Shortened overall length of stay of patients treated with isavuconazole due to less side-effects compared to control patients (e.g. less nephrotoxicity, drug-drug interactions)
- Overall cost-savings by using isavuconazole (e.g. due to a shortened overall length of stay)
- Isavuconazole may increasingly play a major role in treatment of rare IFDs

Data Collection

The data collection process will be compliant with all applicable European, German national, and German federal data protection regulations, including EU directive 2016/679 and the German DS-GVO. eCRFs will be provided using the ClinicalSurveys.net online platform of UHC. ClinicalSurveys.net is hosted by QuestBack, Oslo, Norway on servers in Cologne, Germany as part of a software-as-a-service agreement. The proprietary software allows rapid design and deployment of electronic CRFs. Investigators from participating study sites log into the system with username and a safe password including letters, numbers, and symbols. All investigators can only view and modify their own contributions. All data transmissions are encrypted via TLS 1.2 with an AES 256 GCM bit key and ECDHE RSA key exchange; certificate provided by COMODO RSA Domain Validation Server. Data is only documented anonymously, no directly identifying data are stored on QuestBack servers.

Administration of the eCRF is limited to selected and named administrators at UHC, who receive comprehensive training in the system before access is granted. Secure passwords are also enforced for administrators and they have to regularly change their passwords. Any data manipulation by users and administrators is logged in an audit trail allowing complete data reconstruction. Server

administration is performed by QuestBack, and includes regular updates of the linux-based servers, rigid firewall configuration, current virus and threat detection, and daily backups (on-site and off-site with secure storage).

Contracts between UHC and QuestBack regulate ownership and responsibility for data and eCRFs. Regular on-site audits of security and data protection measures are performed at QuestBack Cologne by UHC. The platform has been extensively used in hundreds of surveys and studies and has received approval by the responsible data protection officers at UHC. Chart abstractors will be experienced and trained for this study. An abstraction manual will be developed as a companion to the eCRF and will be integrated as automated guidance for the abstractor. The eCRF will be pilot tested at the UHC before deployment to the other participating centers.

Maintaining Anonymity

The study will maintain full anonymity of patients for all study procedures. Specific measures to ascertain effective deidentification will be:

- All database IDs will be generated at random and centers will not maintain a list of connecting database IDs with patient names or pseudonyms. All communication between the data management and centers will be on a general level of data quality after central monitoring of data.
- AEs, SAEs and all other reports to the sponsor will not contain any identifying information on individual patients. The sponsor will receive a notification of the reported event (only in relationship with the drug isavuconazole), the reporting person and the site. It will be duty of the sponsor to contact the site and ask for additional information based on regular reporting duties between physicians and pharmaceutical companies.
- While documentation is comprehensive, several measures are taken to protect against any attempts of re-identification:
    - No exact dates will be collected, only year and season of treatment. Timing of events is documented in relative numbers.
    - All data items are documented in as broad as possible categories for the purpose of the study hypothesis.
    - No phenotypical information, e.g. loss of limbs, facial patterns etc. will be recorded.
- Taken together, reidentification of individual will not be possible in most cases and would require direct access to the complete patient files of the treating hospital. Therefore, no additional privacy risk for the patient is caused by documentation for this study.

Ethical and Regulatory Considerations

Health data protection laws of the German states allow anonymous data transmission without explicit patient consent, e.g. §6 health privacy protection law of the state of North Rhine-Westphalia. This also applies to most European countries. No identifying characteristics of patients will be documented throughout this study. The study fulfills criteria of an observational study ("Anwendungsbeobachtung") according to §67 (6) of German drug law, which is why we will contact competent authorities and the organizations of the German health insurances whether they wish to receive the protocol and a list of participants. No study interventions will take place throughout this study.

Final Report

Following data documentation and statistical analysis, study results will be presented in a final report. A publication in a peer-reviewed journal is also intended. Additionally, (preliminary) results will be presented on national and/or international scientific conferences (e.g. ECCMID, ID Week, KIT).

Schedule

- Setup database, draft protocol: 04/2021 – 07/2021
- Setup study participating sites: 08/2021 – 10/2021
- Documentation: 11/2021 – 03/2022
- First statistical analysis & abstract: 04/2022 – 06/2022
- Statistical analysis & final report: 07/2022 – 10/2022

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