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Safety Evaluation of Linear and Macrocyclic Gadolinium-Based Contrast Agents for Patients with Mild to Moderate Renal Insufficiency Undergoing Enhanced Magnetic Resonance Imaging (Interventional Prospective Study) Clinical Trial Protocol

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Informed Consent Form•Informed Page

Dear Sir / Madam,

We will invite you to participate in a clinical trial of "Safety Evaluation of Linear and Macrocyclic Gadolinium Based Contrast Agents for Patients with Mild to Moderate Renal Insufficiency Undergoing Enhanced Magnetic Resonance Imaging".

Before you decide whether to participate in this study, please read the following as carefully as possible. It can help you understand the content of the study, why this study was conducted, and the benefits, risks and discomforts that this study may bring to you. This study has passed the review of the medical ethics committee of Lishui Central Hospital, and is in compliance with the relevant Chinese laws and regulations, Helsinki Declaration and other ethical principles to protect the rights and interests of subjects.

Research Introduction

1. Research background

The principle of magnetic resonance imaging (MRI) depends on the magnetic field produced by water molecules in human body. It has many advantages, such as high resolution of soft tissue (such as nervous system, parenchymal organs and muscle tissue), using non ionizing electromagnetic radiation, no known exposure risk, and many imaging parameters (sequence, proton density, T1 and T2 relaxation time). Since used in clinical in 1980s, it has been clinically proved to be a valuable imaging diagnosis method. In the early clinical practice, MRI was mainly used in plain scan, but the value of contrast-enhanced magnetic resonance imaging (CE-MRI) in the diagnosis of diseases was not recognized. In the later stage, CE-MRI has become an important supplement to MRI because of its advantages in the diagnosis of small lesions, inflammation, edema and tumors. At least 30% of diseases need MRI contrast agent injection.

In 2000, Cowper described the mucoedema-like sclerosis skin disease of renal

dialysis patients in the Lancet magazine, that is, late-stage nephrogenic systemic fibrosis (NSF). In 2006, Grobner reported the induction of nephrogenic skin disease or NSF. The factor may be gadolinium. In the same year, Marckmann discovered that NSF may be caused by the use of gadolinium diamine during MR examination. Due to the serious harm of NSF, foreign scholars began to pay attention to the relationship between gadolinium contrast agent and NSF, and aroused clinical attention to the safety of gadolinium contrast agent. Subsequently, the European Society of Urology and Radiology (ESUR) classified gadolinium contrast agent as high-risk, medium-risk and low-risk. , And use gadolinium contrast agent according to renal function classification, after that, new NSF reports gradually decreased to disappear. Due to the long-term concern about the safety of gadolinium contrast agent, Dr. Tomonori Kanda from the Hyogo Cancer Center in Japan published an article in Radiology in 2014 and explained for the first time the relationship between the high signal of T1 in the dentate nucleus and globus pallidus and the deposition of gadolinium. In 2015, Dr. Robert J. McDonald and Kanda from the Mayo Medical Center in the United States published an article in the Journal of Radiology at the same time and confirmed the presence of gadolinium deposits in the brain through an autopsy. Later, foreign scholars paid great attention to the phenomenon of gadolinium contrast agent and gadolinium deposition in the brain. Some scholars believe that the brain gadolinium deposition (dentate nucleus hyperintensity) is caused by linear contrast agent instead of large ring, but some scholars believe that large ring may also It caused the deposition of gadolinium in the brain. After reviewing many evidences, in order to avoid potential harm, the European Medicines Agency (EMA) finally decided in July 2017 to restrict the application of some linear gadolinium contrast agents to humans.

At present, the GBCA approved by the China Food and Drug Administration (CFDA) includes gadopentetate meglumine, gadolinium diamine, gadolinium fuseamide, gadolinium benzamide, gadolinium disodium gadolinate, and gadolinium. Butrol,

gadoterol and gadoterate meglumine. Due to the harm or potential harm of nephrogenic Systemic Fibrosis (NSF) and Gadolinium deposition disease (GDD) to the human body, the US Food and Drug Administration (FDA) prohibits partial linearity GBCA (such as gadolinium diamine, gadopentetate meglumine) is used for special populations (eGFR<30 ml/min/1.73m^2, acute kidney injury), while the European Medicines Agency (EMA) prohibits some linear GBCA Intravenous (such as: gadolinium diamine, gadopentetate meglumine) for human body enhancement. Since the stability of large ring GBCA is better than linear GBCA, FDA and EMA do not make special requirements. Gadoterate Meglumine (Gadoterate Meglumine, Gd-DOTA) are all macrocyclic GBCA. Gd-DOTA is the only ionic macrocyclic gadolinium contrast agent with the best stability (stable conditions) Constant, dissociation half-life, chelation residue and other parameters evaluation), is also the only large ring gadolinium contrast agent included in the national medical insurance catalog.

Contrast agent-type allergic reactions are difficult to predict and sudden, while acute adverse reactions in allergic-like reactions are not only difficult to predict and sudden, but can also lead to shock and death of patients, seriously disturbing radiologists and causing serious work pressure. In this study, the safety evaluation of linear and macrocyclic gadolinium based contrast agents for patients with mild to moderate renal insufficiency undergoing enhanced magnetic resonance imaging provides a basis for the selection of gadolinium for clinical CE-MRI examinations in such patients.

2. Research purpose

This study aims to evaluate the safety of linear contrast agent (gadodiamide) and macrocyclic gadolinium based contrast agents in patients with mild to moderate renal insufficiency when performing CE-MRI examinations, and to provide the optimal gadolinium selection plan for patients with renal insufficiency.

3. If I participate in the study, what will I need to do?

If you meet the selection criteria and agree to participate, the study will be

conducted as follows:

1) The doctor will inform you and your family members of the possible adverse reactions and risks of contrast injection before the examination. You need to sign an informed consent form. After confirming the enrollment, you will be randomly assigned to the linear group (ie CE-MRI with gadolinium diamine injection as a contrast agent) or circular group (ie CE-MRI with gadoterate meglumine injection as a contrast agent)).
2) After you inject the gadolinium based contrast agent, you will be followed up for the next 60 minutes, 1h-1w, and 3 months to complete the necessary test indicators. If an adverse reaction occurs during this period, please contact the research doctor in time, and the doctor will make corresponding treatment measures based on your condition.

4. What are the eligibility criteria?

1) Inclusion Criteria:

i. Patients aged 18 to 80 years old who require gadolinium based CE-MRI;

ii. Patients with renal function 30ml/min/1.73m^2≤eGFR＜90/min/1.73m^2;

iii. Patients who are able and willing to comply with the required inspection requirements.

2) Exclusion Criteria:

i. Patient who experienced allergic reactions to previous gadolinium based contrast agents;

ii. Patient who had used gadolinium based contrast agents within 3 months;

iii. Patient with acute renal failure;

iv. Patient who cannot comply with or cannot tolerate the necessary fluid replenishment procedures; 5.Patient with major mental illness, impaired consciousness or other diseases considered by researchers to affect observation.

5. If you participate in this study, what will you benefit?

By participating in this study, you will benefit from additional medical attention and guidance from both medication and lifestyle. Also, during the next 2 years of follow-up, if you have any questions about treatment or condition, you can always consult the research doctor or research coordinator. They will carefully monitor your condition and treatment, and answer your related questions.

Secondly, if you participate in this study, if you are assigned to the experimental group, you will use gadoteric acid meglumine salt injection for free. You have contributed to medical research on the practice of contrast agents, and other patients may also benefit from the information gained from this study.

6. What are the risks of my participation in the study?

Gadolinium based contrast agents are widely used in enhanced magnetic resonance examinations. According to incomplete statistics, there are about 34 million MRI examinations worldwide each year, and about half of them use intravenous injection of gadolinium contrast agents. A large number of phase I-IV clinical trials of drugs have confirmed that compared with iodine contrast agents, gadolinium contrast agents have the characteristics of small dosage and low incidence of adverse reactions. The results of many studies have shown that the incidence of acute adverse reactions of intravenous gadolinium contrast agent is about 0.02%-2.4%. Headache, nausea, taste changes, and urticaria are common acute adverse reactions, which can be relieved by symptomatic and supportive treatment. Severe anaphylactic shock rarely occurs (incidence rate is about 0.004%-0.01%). A very small number of patients will have delayed adverse reactions. Renal systemic fibrosis (NSF) is one of them. A study in the United States confirmed that the probability of NSF after intravenous injection of gadolinium contrast agent is about 0.01%. The incidence of kidney transplant patients increased significantly, 1% and 0.8%, respectively.

The gadolinium based contrast agents used in this study are gadolinium diamine injection (OMNISCAN, General Electric Pharmaceutical (Shanghai) Co., Ltd.) and gadoterate meglumine injection (jiadixian, Jiangsu Hengrui Pharmaceutical Co., Ltd.).

Both of the two gadolinium based agents are commonly used after they are marketed, and they have good safety.

During the trial, there may be some other discomforts, please tell your study physician immediately, he/she will deal with your discomfort.

7. Will participating in this study increase my medical expenses?

The laboratory examinations in this study are based on clinically necessary examination items. There are no additional examinations or paid items. Participating in this study will not increase your medical expenses.

8. Compensation for damage

If you participate in this study, the treatment costs for patients with gadoterate meglumine who have serious adverse reactions related to the product (dyspnea, severe bronchospasm, severe laryngeal edema, seizures, shock, hypertension, death, etc.) , Jiangsu Hengrui Pharmaceutical Co., Ltd. will make compensation and compensation in accordance with relevant national laws and regulations.

9. Is personal information confidential?

The information about your participation in this study will be recorded in the study medical record/case report form. All test results (including personal data, laboratory test documents, etc.) appearing in the original medical records will be completely confidential to the extent permitted by law. Your name will not appear in the CRF form, only your initials in pinyin and the number assigned when you participated in the trial. In relevant research summaries, articles, and public publications, if necessary, only your initials and number will appear.

When necessary, the drug regulatory department, ethics committee or project funding department can consult the data of the subjects participating in the research as required. But without permission, they will not use the data of the participants in the study for other purposes or disclose it to other groups.

10. How can I get more information?

If you have any questions about this trial study at any time, please consult Dr. Chenying Lu at 0578-2285502.

If there is any important new information during the trial that may affect your willingness to continue participating in the study, your doctor will notify you in time.

11. Do I have to participate in this research?

Whether to participate in this study is entirely up to your volition, you can refuse to participate in this study.

12. Can I withdraw from this test halfway?

At any time during the research process, you have the right to withdraw from this research. If you choose to withdraw from this study, your benefits will not be affected, and you will not be discriminated against or retaliated against. If you choose to participate in this trial, we hope that you will continue to complete the entire trial process.

Your doctor or investigator may suspend your participation in this trial at any time for your best interests.

If you withdraw from the trial for any reason, you may be consulted about your use of the trial drug. You may also be asked for laboratory tests and physical examinations if the doctor thinks it is necessary. You can also refuse, and you will not be discriminated against or retaliated against.

13. What do we do now?

Whether to participate in this pilot study is up to you. You can make a decision after discussing it with your family or friends.

Before you make a decision to participate in the trial, please ask your doctor about the relevant questions as much as possible until you fully understand the trial study.

Informed Consent Form•Consent Signature Page

Consent statement

1. I have read this informed consent form, and the person in charge of the project has explained the purpose, content, risks and benefits of this experiment to me in detail.
2. I have discussed and asked related questions about this research, and the answers to these questions are satisfactory to me.
3. I have enough time to make a decision.
4. I voluntarily agree to participate in the clinical research described in this article.
5. If I withdraw halfway due to this product, I will tell the doctor about the changes in my condition in time.
6. If I need to take any other treatment due to changes in my condition, I will seek the advice of the doctor in advance or tell the doctor truthfully afterwards.
7. I agree to the representative of the drug regulatory department, ethics committee or project funding department to consult my research data.
8. I will get a signed and dated copy of the informed consent form.

Finally, I decided to agree to participate in this experimental study and promise to follow the doctor's advice.

Subject's signature:_____ Date(MM/DD/YYYY): _____

Subject's contact number: _____

I confirm that I have explained to the subject the details of the study, including their rights and possible benefits and risks, and gave them a copy of the signed informed consent.

Doctor's signature:_____ Date(MM/DD/YYYY): _____

Study doctor contact information: _____

(This page is a necessary part of the subject's informed consent form. Each "subject's informed consent form" must have the signature and date of the subject/legal representative and research doctor to be valid.)