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Protocol for thiamine and folic acid in the treatment of cognitive impairment in maintenance haemodialysis patients: a prospective, randomised, placebo-controlled, double-blind, multicentre study

Renhua Lu ,[1] Le-Yi Gu,[1,2] Weiming Zhang,[1] Yongping Guo,[3] Xiujuan Zang,[4] Yan Zhou,[5] Ling Yu,[6] Shuting Pan,[2] Huihua Pang,[1] Shang Liu,[1] Kewei Xie,[1] Ping Li,[1] Xiaojun Zeng,[1] Yifei Lu[7]

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For numbered affiliations see end of article.

Correspondence to
Dr Le-Yi Gu; guleyi@aliyun.com

ABSTRACT

Introduction Cognitive impairment (CI) is the common complications in maintenance haemodialysis (MHD) patients. Recently, the pathogenesis of CI has been discussed and oxidative stress is one of the main mechanisms in these patients. Thiamine and folic acid, which play an important role in relieving the production of reactive oxygen species, reducing homocysteine levels, improving oxidative stress in the nervous system. In pilot study, cognitive function was significantly improved in the group with thiamine and folic supplementation. Based on this result, we hypothesise that thiamine combined with folic acid supplementation may improve cognitive function in patients with MHD.

Methods and analysis In this prospective, randomised, placebo-controlled, double-blind, multicentre study, we will enrol patients undergoing haemodialysis who has the Montreal Cognitive Assessment score lower than 26 to treatment group (thiamine 90 mg/day combined with folic acid 30 mg/day) or control group (thiamine placebo 90 mg/day combined with folic acid placebo 30 mg/day). All subjects will be followed up for 96 weeks. The primary endpoint is the comparison of Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) score between treatment group and control group at 96 weeks of follow-up. The secondary endpoints include serum thiamine, folate, homocysteine levels, cranial functional MRI and survival. The central randomisation method will be adopted and the principles of placebo-controlled, double-blind randomised control will be followed. The comparisons among ADAS-Cog scores and other secondary endpoints over time within subjects is conducted by using repeated measure analysis of variance (ANOVA) or generalised estimating equations (GEE). Pairwise t-test with Bonferroni adjustment is performed for multiple comparisons. On the other hand, for comparisons between treatment and control group, simple one-way ANOVA, GEE or Wilcoxon rank sum test is used. The χ^2 method is used for statistical analysis of the categorical data. Kaplan-Meier survival curve is used for survival analysis. A $p<0.05$ is considered statistically significant difference.

Ethics and dissemination This trial has been approved by Shanghai Jiao Tong University School of Medicine, Renji Hospital Ethics Committee (KY2019-199). After publication of study results, trial report will be published in peer-reviewed journals and/or in national or international conferences.

Trial registration number ChiCTR2000029297.

Strengths and limitations of this study

- This is a prospective, randomised, placebo-controlled, double-blind, multicentre study in maintenance haemodialysis patients addressing the complication of cognitive impairment.
- The trial includes treatment and control group.
- It provides important 96 weeks data on cognitive function, serum thiamine, folate, homocysteine levels, cranial functional MRI and mortality.
- Laboratory test and adverse events are closely monitored to ensure the safety of the study during follow-up.
- Although unified training is conducted, cognitive score measurement by different researchers may differ in the evaluation of cognitive function of subjects in a multicentre study.

INTRODUCTION

This publication describes the study design and protocol of a clinical trial on thiamine and folic acid in the treatment of cognitive impairment (CI) in maintenance haemodialysis (MHD) patients: A prospective, randomised, placebo-controlled, double-blind, multicentre study (V.2.0; Date 8 May 2020).

Background

CI is one of the common neurological complications in patients with end stage renal disease (ESRD).[1] Our previous single-centre cohort observational study showed that the incidence of CI in patients with MHD was 51.6%.[2]

As we know, acute neurological complications such as stroke which is taken seriously concern by nephrologist. However, CI may be ignored in patients on MHD by nephrologist. At the same time, because of the dormant clinical symptoms in early CI patients, this complication can not be timely diagnosed and treated, significantly reduce the patient's quality of life, and leads to the poor clinical prognosis. These bring to the country's social and family burden which need to cause the extensive concern of the medical profession.

In our single-centre randomised controlled pilot study, 50 MHD patients with CI were enrolled, including the treatment group (n=25, thiamine 90 mg/day combined with folic acid 30 mg/day) and the control group (n=25, nonintervention). After 2 years of follow-up, cognitive function was significantly improved in the treatment group. The 2-year survival rate was also found to be better in the treatment group than in the control group. In addition, there was no statistically significant difference in safety between two groups.

Based on the results of this pilot study, we hypothesise that thiamine combined with folic acid supplementation may improve cognitive function in patients with MHD and provide a prognostic benefit. This needs to be confirmed by a larger sample size randomised controlled multicentre clinical study.

Rationale

Recently, the relationship between cognitive dysfunction and oxidative stress has been discussed in chronic kidney disease patients, especially dialysis patients.[1] Our previous animal study found that the cognitive function of uraemia rats which was assessed by the radial arm water maze test decreased compared with the sham operation group. Histological assessment suggested indicated increased oxidation in the hippocampal neurons and decreased numbers of neurons compared with control mice. This finding is similar to previous studies.[3]

Thiamine and folic acid belong to the family of water-soluble B vitamins.[4] Thiamine is vitamin B_1, which plays an important role in reducing the production of reactive oxygen species in the nervous system and alleviating oxidative stress as the cofactor of transketolase.[5 6] Folic acid, is also called as vitamin B9, involved in the synthesis of purine and thymine, metabolism of amino acid, as well as haemoglobin (Hb) production. Folic acid has a direct antioxidant effect, interacts with endothelial nitric oxide synthase, and affects the bioavailability of nitric oxide cofactors. Moreover, folic acid is essential for the metabolism of homocysteine into methionine, which can reduce homocysteine levels.[7]

More important, clinical studies have reported that the application of vitamins B including thiamine and folic acid can reduce the level of oxidative stress index including homocysteine in blood,[7 8] thereby reducing oxidative stress and bringing benefits to the treatment of cardiovascular complications in patients with ESRD,[9] particularly in those intensive treatment or with a drop in homocysteine levels of more than 20%.[8] Nevertheless, recent systematic review and meta-Analysis indicated that thiamine or folic acid alone can not improves cognitive function healthy older people.[10 11]

However, it is not clear whether supplementation with thiamine and folic acid, can improve cognitive function in ESRD patients? Therefore, we designed this prospective, randomised, placebo-controlled, double-blind, multicentre trial to explore whether the intensive combination of thiamine and folic acid can improve cognitive function in MHD patients with CI. The dose of thiamine (90 mg/day) is according to the treatment dose of Wernicke's encephalopathy[12] and refeeding syndrome.[13] The dose of folic acid (30 mg/day) is refer to the treatment of cardiovascular complications in MHD patients.[8]

Objectives

The primary objective of this trial is to verify the hypothesis that thiamine combine with folic acid supplements can improve cognitive function and prognosis in MHD patients with CI, and to provide evidence based for clinical treatment of this complication.

Trial design

This is a prospective, randomised, placebo-controlled, double-blind, multicentre trial. It has two parallel groups with equal allocation including treatment group (thiamine 90 mg/day combined with folic acid 30 mg/day) and control group (Thiamine placebo 90 mg/day combined with folic acid placebo 30 mg/day). The random envelope method was used for centre randomisation. We used the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines[14] in the current study.

METHODS AND ANALYSIS

Study setting

The current trial will be carried out simultaneously in three centres, Renji Hospital, School of Medicine, Shanghai Jiao Tong University (primary centre), East branch of Shanghai Sixth People's Hospital (sub-centre) and Shanghai Songjiang District Central Hospital (subcentre). In addition, researchers from these three centres have obtained Good Clinical Practice (GCP) certificates.

In total, nearly 600 MHD patients were followed up at Ren Ji hospital. These three centres have a total of about 1000 MHD patients. According to the results of our previous studies, the incidence rate of CI in MHD patients is about 51.6%, so there are enough patients for screening in this study. Patient recruitment will begin imminently and is planned to last 3–6 months.

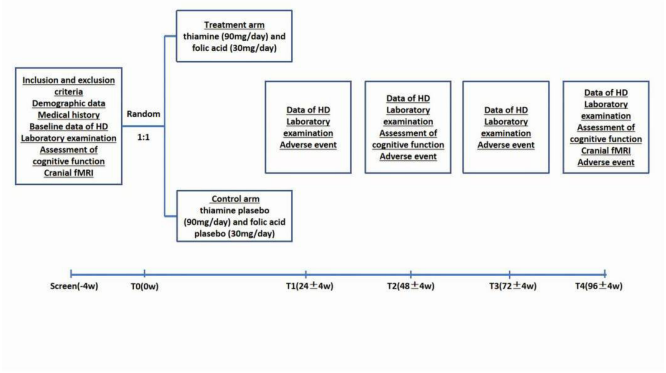

Figure 1 An overview of this trial. fMRI, functional MRI; HD, haemodialysis.

Eligibility criteria

The target population of this study is patients undergoing MHD, who should fulfil the following eligibility criteria.

Inclusion criteria

1. MHD patients (≥3 months).
2. With CI, defined as: Montreal Cognitive Assessment (MoCA) score is less than 26, or MoCA scores is less than 25 if duration of education is less than or equal to 12 years.
3. 18–75 years old, male or female.
4. Sign the informed consent form.

Exclusion criteria

1. Unable to cooperate and complete the study.
2. Life expectancy is less than 1 year.
3. Participated in other clinical trials within 3 months.
4. Accompanied by severe anaemia, infection, tumour, activity bleeding or heart, liver and lung disease.
5. Thiamine or folic acid allergies.
6. Disorders that may cause CI, such as stroke.
7. Pregnant or lactating women.
8. Subjects judged by the investigator to be unsuitable for inclusion in this study.

Intervention

An overview of the trial is provided in figure 1. The researchers screen subjects according to inclusion criteria and exclusion criteria, after which the subject is randomised to the treatment or the control arm by 1:1.

In the treatment arm, the subjects are treated with thiamine tablets (10 mg/tablet, three tablets three times a day, 90 mg/day) and folic acid tablets (5 mg/tablet, two tablets three times a day, 30 mg/day).

In the control arm, the subjects are treated with thiamine placebo tablets (10 mg/tablet, three tablets three times a day, 90 mg/day) and folic acid placebo tablets (5 mg/tablet, two tablets three times a day, 30 mg/day).

All subjects will be followed up every 24 weeks for 96 weeks (table 1). As the trial proceeds, statistical monitoring and concomitant projects may identify need for revisions to the intervention.

Observation item

Demographic data of subjects at baseline will be collected including age (year), gender, height(cm), weight (kg), history of smoking (smoke every day, no matter how many cigarettes), alcohol abuse (drink alcohol every day, no matter how much), history of drug abuse (drug dependence, no matter how much), history of education (year, high school is defined as duration of education is more than or equal to 12 years), income (yuan/year, the annual income is more than or less than ¥30 000), medical expenses (yuan/year), CI family history and work status (full-time or part-time jobs/retire).

The medical history of the patients, such as the primary cause of MHD, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, cirrhosis, chronic obstructive pulmonary disease, the date of initiate dialysis, average weekly urine volume (mL/day), as well as folic acid, vitamin B_{12}, active vitamin D and intravenous iron therapy in the last 6 months will be collected.

The following information of HD treatment will be collected at baseline, 24 weeks, 48 weeks, 72 weeks and

Table 1 The visit schedule of this study

	Screen	Randomisation	Follow-up period			
Visiting period (weeks)		T0	T1	T2	T3	T4
	−4	0	24±4	48±4	72±4	96±4
Informed consent	×					
Inclusion and exclusion criteria	×					
Demographic data	×					
Medical history	×					
Information of haemodialysis	×		×	×	×	×
Laboratory examination	×		×	×	×	×
Cognitive function	×			×		×
Imageological examination	×					×
Drug administration		×	×	×	×	×
Adverse event	×	×	×	×	×	×

96 weeks of follow-up: dialysis duration (h/session), dialysis frequencies (time/week), dialysis modality (HD) or hemodiafiltration (HDF), which is the main dialysis modality, for example, HD twice a week and HDF once a week HD means HD, vascular access (fistula or catheter), average weekly ultrafiltration (L/session), hypotension during dialysis treatment in the last week (definition of hypotension: systolic pressure <90 mm Hg or diastolic pressure <60 mm Hg), use low molecular heparin, weight of pre and post HD (kg), blood pressure of pre-HD and post-HD (mm Hg), heart rate of pre and post-HD (BPM).

Laboratory examination data at baseline, 24 weeks, 48 weeks, 72 weeks and 96 weeks of follow-up, such as white cell count, Hb, platelet, Alanine aminotransferase (ALT), Aspertate aminotransferase (AST), total protein, total bilirubin, PH, HCO_3^-,K^+, Na^+, Cl^-, albumin, total cholesterol, triglyceride, Low density lipoprotein (LDL), High density lipoprotein (HDL), calcium, phosphorus, iPTH, ferritin, fasting blood glucose, C reactive protein, β_2-microglobulin, B natriuretic peptides, thiamine, folic acid and homocysteine will be collected. Transferrin saturation and dialysis adequacy (spKt/V) will be calculated.

Cognitive function including MoCA,[15] Mini-mental state examination (MMSE)[16] and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[17 18] will be assessed at baseline, 48 weeks and 96 weeks of follow-up.

Imageological examination including cranial functional MRI (fMRI) will be performed at baseline and 96 weeks of follow-up.

Endpoints

Primary endpoint

The primary endpoint is the comparison of ADAS-Cog score between the treatment group and the control group at 96 weeks of follow-up.

Secondary endpoints

The secondary endpoint are listed below:

1. The comparison of serum thiamine, folate, and homocysteine levels between the treatment and control groups at 96 weeks of follow-up.
2. The comparison of cranial fMRI between treatment group and control group at 96 weeks of follow-up.
3. Survival comparison between treatment group and control group at 96 weeks of follow-up.

Safety endpoints

Changes in laboratory safety indicators and incidence of adverse events between the treatment and control groups during follow-up.

Withdrawal and drop-out

Shedding criteria

1. The researchers find serious safety problems.
2. The effect is so poor that there was no need to continue the trial.

Exit criteria

1. Subjects who meet the inclusion criteria and do not complete the study for any reason are considered to be withdrawal subjects, which include subjects' self-withdrawal and subjects' withdrawal determined by the investigator.
2. Severe adverse events occurred and the investigator considered it appropriate to withdraw from the study.
3. Major Trial Protocol Deviation Subjects are found to not meet the requirements of the trial protocol after randomisation.
4. Serious other complications occurred during the clinical trial, and the investigators determined that it would not be beneficial to continue the study.
5. Unplanned pregnancy.
6. Lost follow-up, subjects do not return to the centre and contact with subjects failed.

If a subject is lost to follow-up, the investigator should make every effort to contact the subject and encourage the subject to continue to participate in the study as planned. If the subject withdraws their informed consent, the researcher should not evaluate the subject further and should not attempt to collect more data.

For subjects who withdraw from the trial early, the last interview should be arranged within 3 days after the withdrawal (the content of the interview should be determined by the investigator according to the actual situation of the subjects) to complete the efficacy and safety assessment.

Even if the subject is unable to return to the study centre for visits, the investigator will complete all available data on the case report form and record the reason for early withdrawal. Whenever possible, the subject must return all drugs. The investigator will take inventory of the drug and complete the Drug Release and Recall Record Form.

Participant timeline

Please refer to figure 1 for details of the visit schedule and participant timeline.

Sample size and recruitment

Based on the previous single-centre study, it was assumed that cognitive function (MoCA score) in the treatment group improved from 20 to 26, and set alpha=0.05 and 1-beta=0.9, then at least 100 patients per group are required. In consideration of control shedding or rejection rate within 15% during the test and subsequent analysis requirements, 115 cases were planned to be enrolled in each group. The ratio of the treatment group to the control group was 1:1, with 115 cases in the treatment group and 115 cases in the control group. This study will screen and enrol patients on MHD in three research centres.

Randomisation

The central randomisation method will be adopted in this study and the principles of placebo-controlled, double-blind randomised control will be followed. All eligible

subjects will be randomised in a ratio of 1:1 and divided into the treatment and control arms.

Randomisation sequence will be generated by an independent data manager using SAS (V.9.3) and stored within sealed opaque envelopes. The investigator open an envelope to obtain a number every time a patient is consented to enter the trial. Based on this number, the patient is assigned the corresponding number of medication (treatment drugs or placebos).

Blind and unblind

This is a prospective, randomised, placebo-controlled, double-blind, multicentre trial. This study will establish the programme of blind setting and blind breaking. There are both blind and non-blind drug administrators in this study. To ensure the indistinguishable nature of the investigational drug, the blind drug administrator will confirm the indistinguishable nature of the investigational drug and its matching placebo in terms of appearance, taste, etc., before the investigational drug is distributed and unblinded. The non-blind drug administrator creates a master random list of drugs and creates a code break blind authorisation number for emergency code break blind. The non-blind drug administrator will securely store the master random list and the code broken blind authorisation number list until unblinding. The investigator will develop and maintain a written emergency code blinding procedure to be followed in response to an emergency.

Selected data collection methods

Cognitive function scores including MoCA, MMSE and ADAS-Cog will be performed by board certified neurologists whenever possible. All cognitive function scores will be performed before or during the interval of HD.

Data statement

The investigator must properly handle all the data obtained during the clinical trial, and truthfully record all adverse events and serious adverse events during the clinical trial, so as to ensure the rights and privacy of the subjects participating in the clinical trial. Personal information of subjects will be collected, shared and maintained to protect confidentiality during and after the study. Only the project investigator will have access to the final trial data set.

A data monitoring committee is composed of clinicians and biostatisticians from Clinical Centre for Investigation, Renji Hospital, School of Medicine, Shanghai Jiao Tong University who are not involved in this study for the purpose of ensuring the safety of subjects and the quality of study data.

Statistical methods

Data set category

1. Full-analysis set (FAS): the case of using at least once drugs and main efficacy indexes data after the drug administered.
2. Per-protocol set (PPS): the good compliance case of meeting the main inclusion and exclusion criteria without affecting the main curative effect of prohibiting drugs during the trial.
3. Safety set (SS): the case of using the investigational drug product at least once with a safety evaluation.

Statistical analysis technique

It will be listed separately that the number of subjects selected and completed the follow-up in the population and centres, identifying three analysis data sets (FAS, PPS, SS) as specified above. The primary analysis only include patients with completed primary outcomes. The comparisons among ADAS-Cog scores and other secondary outcomes over time within subjects is conducted by using repeated measure analysis of variance (ANOVA) or generalised estimating equations (GEE) and pairwise t-test with Bonferroni adjustment is performed for multiple comparisons. On the other hand, for comparisons between treatment and control group, simple one-way ANOVA, GEE or Wilcoxon rank sum test is used. The χ^2 method is used for statistical analysis of the categorical data. For missing data in secondary efficacy outcomes, they are assumed to be missing at random and multiple imputation was conducted. Kaplan-Meier survival curve is used for survival analysis.

Variables of normal distribution are presented by means with SD while skewed ones are reported as the median and the IQRs. Counting data are expressed as constituent ratios or percentages.

A $p<0.05$ is considered statistically significant difference. Statistical analyses are conducted with SPSS (V.20.0, SPSS).

Harms

Safety endpoints relate directly to changes in laboratory safety indicators and incidence of adverse events between the treatment and control groups during follow-up. These endpoints will be listed according to treatment received with a breakdown. Subjects will be followed up in detail, if any complications arise, appropriate treatment will be provided in accordance with current routine medical procedures.

Patient and public involvement statement

The trial protocol was developed in part by nephrological and neurological physicians with years of experience in treating MHD patients with CI. At the same time, medical statisticians performed study design and sample size estimation. Patients and the public have not yet been involved directly in the design, or conduct, or reporting, or dissemination plans of this trail protocol.

Ethics and dissemination

This trial has been approved by Shanghai Jiao Tong University School of Medicine, Renji Hospital Ethics Committee (KY2019-199). Other participating subcentres must also obtain ethics committee approval documents prior to the start of clinical trials. The GCP[19] regulations shall be strictly followed during the test implementation. Amendments to the protocol will be reviewed by ethics

committees. Informed consent will be obtained before collecting any patient data and patient information. After publication of study results, trial report will be published in peer-reviewed journals and/or in national or international conferences. All researchers involved in the design, discussion and writing of this study protocol, as the authors.

DISCUSSION

Epidemiological study shows the number of dialysis patients is expected to rise to 2.162 million by 2030 in Asia.[20] Meanwhile, CI is a common complications in ESRD patients.[1] In pilot study, we enrolled 50 MHD patients with CI, including the treatment group (n=25) who received thiamine 90 mg/day combined with folic acid 30 mg/day and the control group (n=25) who was the blank control group. After 2 years of follow-up, cognitive function which was evaluated by MOCA score was significantly improved in the treatment group. In addition, there was no statistically significant difference in safety between the two groups.

Based on the results of this pilot study, we designed this prospective, randomised, placebo-controlled, double-blind, multicentre trial. In this study, MHD patients with CI from several large-scale HD centres in Shanghai will be enrolled in a prospective, randomised, controlled, double-blind study. According to the sample size of the pilot study, 230 subjects will be expected to be enrolled. The subjects will be randomly divided into treatment group (n=115, thiamine 90 mg/day combined with folic acid 30 mg/day) and control group (n=115, thiamine placebo 90 mg/day combined with folic acid placebo 30 mg/day) and followed up for 96 weeks. Cognitive function scores, serum levels of thiamine, folate and homocysteine, fMRI of the brain, and safety measures will be monitored regularly.

This study hopes to verify added thiamine and folic acid reduces homocysteine levels, so as to relieve the oxidative stress and improve cognitive function in patients with MHD. To explore the benefits of supplementation with thiamine and folic acid in the prognosis of MHD patients with CI. To evaluate the safety of thiamine and folic acid in MHD patients. This study may provides evidence-based evidence for the clinical treatment of this complication and ultimately lays a foundation for the organisation and implementation of higher level clinical research in this field.

This exploratory study would be conducted to evaluate the efficacy of thiamine and folic acid supplement in the treatment of MHD patients complicated with CI, so as to help clinically find an effective treatment for this complication and reach the leading domestic and international level. It is helpful to promote the cross-collaboration and common development of multicentres and multidisciplines, improve the ability and level of the treatment of nervous system complications in MHD patients, and lay a foundation for the organisation and implementation of higher level clinical research in this field.

Through this study, a breakthrough can be achieved in the treatment of MHD patients complicated with CI, blocking the disease progression of MHD patients, reducing the hospitalisation rate, medical costs and mortality of MHD patients caused by CI, improving the quality of life of MHD patients, thus improving the prognosis, and having a good clinical application prospect.

Author affiliations
[1]Department of Nephrology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[2]Clinical Center for Investigation, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[3]Department of Nephrology, Shanghai Sixth Peoples Hospital, Shanghai, China
[4]Department of Nephrology, Shanghai Songjiang District Central Hospital, Shanghai, China
[5]Department of Radiology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[6]Department of Neurology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[7]Department of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai, China

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Contributors RL and L-YG were responsible for the design of the entire study, including the drafting, revision and submission of clinical trial protocols. WZ, YG, XZa, HP, SL, KX, PL and XZe are responsible for the discussion and revision of clinical trial protocol. YZ is responsible for designing the imaging tests. LY takes charge of the design of cognitive function tests. SP is responsible for the design of statistical methods. YL is in charge of the pharmacological mechanisms and dosage selection of experimental drugs. All authors have read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iD
Renhua Lu http://orcid.org/0000-0003-3555-505X

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