Study Protocol

Efficacy and Safety of Prophylactic Treatment for Pneumocystis Jirovecii Pneumonia (PJP) in Patients with Autoimmune Inflammatory Rheumatic Disease (AIIRD)

Version date: 2024.07.04

Background

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection that occurs in immunocompromised patients. The typical clinical symptoms include fever, cough, and dyspnea, with a rapid onset and progression to hypoxemia and even respiratory failure. PJP can be divided into HIV-associated PJP and non-HIV PJP [1-2]. In recent years, with the increasing use of iatrogenic immunosuppressants, the incidence of PJP in non-HIV patients has risen, particularly among patients with autoimmune inflammatory rheumatic diseases (AIIRD), such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathies, and systemic vasculitis [3]. The incidence of PJP in AIIRD patients ranges from 0.7% to 2%, significantly higher than in the general population [4]. In addition, AIIRD patients with PJP are prone to progress to respiratory failure, with severe symptoms, poor prognosis and high mortality. Early identification and prophylactic treatment of PJP could improve outcomes and reduce mortality [5].

Currently, identifying PJP in AIIRD patients is challenging due to overlapping clinical features, such as fever and lymphopenia, and the reduced detection rates of Pneumocystis in respiratory specimens due to immunosuppressant use. Early warning based on serological markers offers a new approach for identifying PJP in AIIRD patients [6-8]. Although there are guidelines for preventing PJP in HIV patients, hematologic malignancies, and solid organ transplant recipients [9-10], no consensus guidelines exist for AIIRD patients on immunosuppressive therapy. More clinical evidence is needed to develop evidence-based clinical guidelines for prophylactic treatment of PJP in AIIRD patients.

This prospective controlled study will use machine learning and other information technologies to analyze clinical data from AIIRD patients. By fitting early clinical indicators (e.g., symptoms, laboratory results) with PJP infection and outcomes, combined with our center's predictive model (combination factor 1 = IgA – IgM × 2.072/1.411) and international consensus and expert recommendations on PJP prophylaxis [11-17], we aim to establish new screening criteria for high-risk populations, and stratified analysis was performed based on risk factors. We'll assess the efficacy

and safety of prophylactic treatment (TMP/SMZ) for PJP in AIIRD patients, explore the AIIRD populations that benefit the most from prophylactic treatment and evaluate the benefit-risk ratio of prophylactic treatment in AIIRD patients, aiming to achieve early identification and guidance for prophylactic treatment, ultimately reducing PJP incidence and improving outcomes in AIIRD patients.

Objectives

1. Develop and validate a predictive model for PJP infection risk in AIIRD patients to facilitate risk stratification, enhanced monitoring, and early prophylactic treatment.
2. Investigate the impact of prophylactic treatment on the incidence and outcomes of PJP in AIIRD patients, evaluating the efficacy, safety, and benefit-risk ratio of prophylactic treatment.

Study design

This study will prospectively collect peripheral blood, respiratory specimens, and clinical data from AIIRD patients, analyze the biological data, establish clinical prediction models, identify high-risk PJP populations among AIIRD patients and administer prophylactic trimethoprim-sulfamethoxazole (TMP/SMZ) treatment. The efficacy and clinical utility of the PJP infection risk prediction model will be validated, and the impact of prophylactic anti-PJP treatment on incidence and outcomes will be explored.

Selection of AIIRD patients

1. Inclusion criteria

a) Diagnosed with AIIRD according to international classification criteria and receiving corticosteroid or immunosuppressant therapy;
b) No prior standard PJP treatment, including first-line TMP/SMZ or other

second-line treatments;

c) Age ≥ 18 years;

d) Informed consent signed for biological sample collection.

2. Exclusion criteria

a) Significant health issues, including (but not limited to) the following: Patients with severe liver injury (elevated serum aminotransferase (ALT, AST), more than 5 times the normal value), severe renal insufficiency (GFR < 30mL/min or Scr > 445umol/L), severe myelosuppression (Hb < 65g/L, PLT < 25×10^9/L or neutrophil < 0.5 x 10^9/L);

b) Screening of known when infected with human immunodeficiency virus (HIV), over the past five years with lymphoid tissue proliferative disease or any organ system malignant tumor medical history, history of solid organ transplant patients;

c) History of sulfonamide allergy or folate deficiency-related megaloblastic anemia;

d) Pregnant and lactating women;

e) Any medical or psychiatric condition that the investigator believes would prevent the trial participant from adhering to or completing the study according to the protocol;

f) Patient refused to comply with the requirements of this study to complete the work.

Sample size estimation

It is expected to prospectively collect a total of 800 patients diagnosed with AIIRD in our hospital. Based on the previous literature and the experience data of our center, there were large differences in some tested indicators in some subgroups. Because involved in machine learning, the required number of samples roughly follows the http://blog.csdn.net/uestc_c2_403/article/details/72859021 url provided by the algorithm, which is about 10 times the number of dimensions + 1. Prospective data expected into the analysis of the parameters/index for 70. Considering that about 10-20% of patients may have missing data in real-world practice, the final sample size

for prospective collection was 70*1.2*10≈800.

Study process

1. Enrollment criteria and patient recruitment

a) Define enrollment criteria and recruit eligible AIIRD patients.

b) Explain the study purpose and obtain written informed consent.

2. Construct a clinical prediction model and recognize PJP high-risk patients

a) The prediction model was established by combining the developed prediction model (combination factor 1= IgA-IgM × 2.072/1.411) with clinically recognized risk factors (including long-term use of high-dose corticosteroids, combination of immunosuppressants, and pulmonary diseases).

b) According above criteria, AIIRD patients with high risk or low risk of PJP are recognized.

3. Grouping and Experimental Intervention

a) Prospectively, we group AIIRD patients into high-risk and low-risk based on the prediction model, and they are further divided into 4 groups according to the intention-to-treat principle: high-risk group 1 (Patients intend to treat with prophylactic TMP/SMZ), high-risk group 2 (Patients intend to treat without prophylactic TMP/SMZ), low-risk group 1 (Patients intend to treat with prophylactic TMP/SMZ), low-risk group 2 (Patients intend to treat without prophylactic TMP/SMZ).

c) Trimethoprim-sulfamethoxazole intervention regimen: TMP/SMZ 480mg po qd (one tablet per day, oral); Treatment time: routine ≥28 days (according to the needs of the patient's condition, as well as the patient's tolerance to the drug and the willingness to treat, the clinician will adjust the time).

4. Follow-up and data collection

a) Establish a long-term follow-up to collect each clinical data on a regular basis. Study visits were set at baseline, 6 and 12 months after the initiation of treatment. The

end points of follow-up were PJP infection, occurrence of serious side effects, death, loss to follow-up, end of follow-up, or withdrawal from the study. Main outcome indicator is pneumocystis infection incidence, and secondary indicators include TMP/SMZ related adverse events, PJP related mortality, other prognostic indicators and parameters of the respiratory system.

5. Statistics and data analysis

a) Using difference test statistical analysis methods such as comparing two main outcome indexes between the groups of patients. Possible confounding factors, such as age, gender, and baseline conditions, were considered in the analysis, and covariates were adjusted if necessary.

b) Statistical analysis methods (such as ROC curve, calibration plot, DCA curve, etc.) were used to evaluate the prediction model performance and visual display (Nomogram, etc.).

c) Stratified according to risk factors, the absolute risk difference of PJP between the control and prevention groups was calculated, and the NNT was calculated based on the risk difference. The bootstrap method is used to estimate NNT and NNH 95% confidence interval (95% CI), for different people to undergo preventive SMZ/TMP risk-benefit assessments.

Possible risks and preventive measures

a) Possible risks: (1) When peripheral blood samples are obtained from patients, some patients may have dizziness and other symptoms due to their physical weakness. (2) When obtaining induced sputum or bronchoalveolar lavage fluid from patients, some patients may have the risk of bronchospasm and asthma induction because they cannot tolerate it. (3) Adverse reactions of TMP/SMZ (such as rash, fever, purpura, nausea and vomiting, leukopenia, elevated transaminase, etc.) occurred during the treatment.

b) Preventive measures: (1) Professional medical staff should take care of the blood collection place, assess whether the patient's current health status is suitable for

additional blood collection, and pay close attention to the patient's status during blood collection. The corresponding first aid drugs are stored at the blood collection site for a long time. (2) The respiratory specimen collection place will be attended by professional medical staff, who assessed whether the patient's current health status is suitable for respiratory specimen collection, and pay close attention to the patient's status during the collection process. The corresponding first aid drugs are stored at the collection place for a long time. (3) Follow up the patients' symptoms and signs regularly, and ask them to check the complete blood count, liver and kidney function, and electrolytes regularly. The TMP/SMZ should be stopped at the first appearance of rash or any signs of adverse reactions, and the adverse reactions should be treated with symptomatic treatment (such as anti-allergic, kidney protective, liver protective drugs; If is showing signs of bone marrow suppression, should be given to patients every day leucovorin 5-15 mg, until the hematopoietic function returned to normal, if necessary, can be used to promote red, white needle and boost platelet hormone therapy).

Reference

[1] Sato T, Inokuma S, Maezawa R, et al. Clinical characteristics of Pneumocystis carinii pneumonia in patients with connective tissue diseases[J]. Modern Rheumatology, 2005, 15(3): 191-197.

[2] Sepkowitz K A. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome[J]. Clinical infectious diseases, 2002, 34(8): 1098-1107.

[3] Teichtahl A J, Morrisroe K, Ciciriello S, et al. Pneumocystis jirovecci pneumonia in connective tissue diseases: comparison with other immunocompromised patients[J]. Semin Arthritis Rheuma, 2015, 45(1): 86-90.

[4] Hsu H C, Chang Y S, Hou T Y, et al. Pneumocystis jirovecii pneumonia in autoimmune rheumatic diseases: a nationwide population-based study[J]. Clinical Rheumatology, 2021, 40: 3755-3763.

[5] Hansel L, Schumacher J, Denis B, et al. How to diagnose and treat a patient without human immunodeficiency virus infection having Pneumocystis jirovecii pneumonia? [J]. Clinical Microbiology and Infection, 2023, 29(8): 1015-1023.

[6] Zhao Z, Huang Y, Ming B, et al. Characterization and associated risk factors of Pneumocystis jirovecii pneumonia in patients with AIRD: a retrospective study[J]. Rheumatology, 2022, 61(9): 3766-3776.

[7] Tang G, Tong S, Yuan X, et al. Using routine laboratory markers and immunological indicators for predicting Pneumocystis jiroveci pneumonia in immunocompromised patients[J]. Frontiers in Immunology, 2021, 12: 652383.

[8] Li Y, Ghannoum M, Deng C, et al. Pneumocystis pneumonia in patients with inflammatory[J]. transplantation, 2013, 13(4): 272-9.

[9] Martin S I, Fishman J A. Pneumocystis pneumonia in solid organ transplantation[J]. American Journal of Transplantation, 2013, 13: 272-279.

[10] Kasiske B L, Zeier M G, Chapman J R, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary[J]. Kidney international, 2010, 77(4): 299-311.

[11] Park J W, Curtis J R, Moon J, et al. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids[J]. Annals of the rheumatic diseases, 2018, 77(5): 644-649.

[12] Dureault A, Chapelon C, Biard L, et al. Severe infections in sarcoidosis: incidence, predictors and long-term outcome in a cohort of 585 patients[J]. Medicine, 2017, 96(49).

[13] Ohmura S, Homma Y, Masui T, et al. Factors associated with pneumocystis jirovecii pneumonia in patients with rheumatoid arthritis receiving methotrexate: a single-center retrospective study[J]. Internal Medicine, 2022, 61(7): 997-1006.

[14] Ghembaza A, Vautier M, Cacoub P, et al. Risk factors and prevention of Pneumocystis jirovecii pneumonia in patients with autoimmune and inflammatory diseases[J]. Chest, 2020, 158(6): 2323-2332.

[15] Tsai M J, Chou C W, Lin F C, et al. Pneumocystis jiroveci pneumonia in patients with systemic lupus erythematosus after rituximab therapy[J]. Lupus, Lupus, 2012, 21(8): 914-918.

[16] Furer V, Rondaan C, Heijstek M W, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases[J]. Annals of the rheumatic diseases, 2020, 79(1): 39-52.

[17] Park J W, Curtis J R, Choi S R, et al. Risk-benefit analysis of primary prophylaxis against Pneumocystis jirovecii pneumonia in patients with rheumatic diseases receiving rituximab[J]. Arthritis & Rheumatology, 2023.

Informed consent (Informed information page)

(The version number: V1.0 Release date: 2024.07.04)

Dear subjects:

We will invite you to attend an *Efficacy and Safety of Prophylactic Treatment for Pneumocystis Jirovecii Pneumonia (PJP) in Patients with Autoimmune Inflammatory Rheumatic Disease (AIIRD)* research, this research project leader: Department of Rheumatology and Immunology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology. The research protocol has been approved by the Medical Ethics Committee of Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, and permission has been granted for clinical research.

Before you decide whether to participate in the study, please read carefully the following content as soon as possible. It can help you understand why the study as well as to conduct the research, research procedures and time limit, to participate in research may bring you benefits, risks, and discomfort. If you like, you also can discuss with your relatives, friends, or ask the doctor to give explanation, help you make a decision.

If you are currently engaged in clinical research, please be sure to inform you that your study doctor or researchers. Thank you for your support in this study.

Why is this study conducted?

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection in immunocompromised patients, characterized by fever, cough, and dyspnea, with rapid onset and progression. Recently, PJP infection in AIIRD patients has become a concern, including those with systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathies, and systemic vasculitis. AIIRD patients with PJP are prone to respiratory failure, severe symptoms, poor prognosis, and high mortality rates. Early identification and prophylactic treatment of PJP may improve outcomes and reduce mortality. However, identifying PJP in AIIRD patients is challenging, and no clear guidelines exist for prophylactic treatment in these patients. In order to establish

evidence-based clinical guidelines, this prospective study using machine learning method to analyze AIIRD patients with clinical data, will AIIRD early clinical indicators, such as symptoms, laboratory results and PJP infection and clinical prognosis of end fitting. Combined with the prediction model developed by our center and the international consensus and expert recommendations on PJP preventive medication, new screening criteria for high-risk population was constructed, and stratified analysis was performed based on risk factors. We aim to assess the efficacy and safety of prophylactic treatment (TMP/SMZ) for PJP in AIIRD patients, and explore the benefit-risk ratio of prophylactic treatment in AIIRD patients.

Who will be invited to participate in the study?

1. Inclusion criteria

a) Diagnosed with AIIRD according to international classification criteria and receiving corticosteroid or immunosuppressant therapy;
b) No prior standard PJP treatment, including first-line TMP/SMZ or other second-line treatments;
c) Age ≥ 18 years;
d) Informed consent signed for biological sample collection.

2. Exclusion criteria

a) Significant health issues, including (but not limited to) the following: Patients with severe liver injury (elevated serum aminotransferase (ALT, AST), more than 5 times the normal value), severe renal insufficiency (GFR < 30mL/min or Scr > 445umol/L), severe myelosuppression (Hb < 65g/L, PLT < 25×10^9/L or neutrophil < 0.5 x 10^9/L);
b) Screening of known when infected with human immunodeficiency virus (HIV), over the past five years with lymphoid tissue proliferative disease or any organ system malignant tumor medical history, history of solid organ transplant patients;

c) History of sulfonamide allergy or folate deficiency-related megaloblastic anemia;
d) Pregnant and lactating women;
e) Any medical or psychiatric condition that the investigator believes would prevent the trial participant from adhering to or completing the study according to the protocol;
f) Patient refused to comply with the requirements of this study to complete the work.

The participating units and the expected number of people to be included in the study

This study is expected to prospectively collected a total of 800 cases who diagnosed with AIIRD in Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology.

What will be required if I participate in the study?

1. Before you are enrolled in the study, your doctor will ask for and record your medical history.

If eligible, you can voluntarily participate by signing the informed consent form.

If you don't want to take part in the study, we will comply with your wishes.

2. If you volunteer to participate in the study, the following steps will be taken:
a) Get your age, gender, in the medical record system desensitization (name, ID number, contact information, home address and other personal privacy information of clinical and laboratory and radiographic information);
b) Peripheral blood samples collection; A sample of your induced sputum or bronchoalveolar lavage fluid will need to be obtained for PCR testing of Pneumocystis carinii.
3. Other matters that require your cooperation

None.

Possible benefits of participating in research

Patients are eligible for certain cost reductions; Contribution to the advancement of diagnostic and therapeutic strategies for AIIRD-PJP.

Potential Risks, Discomforts, and Inconveniences

Possible risk: (1) When peripheral blood samples are obtained from patients, some patients may have dizziness and other symptoms due to their physical weakness. (2) When obtaining induced sputum or bronchoalveolar lavage fluid from patients, some patients may have the risk of bronchospasm and asthma induction because they cannot tolerate it. (3) Adverse reactions of TMP/SMZ (such as rash, fever, purpura, nausea and vomiting, leukopenia, elevated transaminase, etc.) occurred during the treatment.

Mitigation Measures: (1) Professional medical staff should take care of the blood collection place, assess whether the patient's current health status is suitable for additional blood collection, and pay close attention to the patient's status during blood collection. The corresponding first aid drugs are stored at the blood collection site for a long time. (2) The respiratory specimen collection place will be attended by professional medical staff, who assessed whether the patient's current health status is suitable for respiratory specimen collection, and pay close attention to the patient's status during the collection process. The corresponding first aid drugs are stored at the collection place for a long time. (3) Follow up the patients' symptoms and signs regularly, and ask them to check the complete blood count, liver and kidney function, and electrolytes regularly. The sulfonamides should be stopped at the first appearance of rash or any signs of adverse reactions, and the adverse reactions should be treated with symptomatic treatment (such as anti-allergic, kidney protective, liver protective drugs; If is showing signs of bone marrow suppression, should be given to patients every day leucovorin 5-15 mg, until the hematopoietic function returned to normal, if

necessary, can be used to promote red, white needle and boost platelet hormone therapy).

Costs

a) Patients are eligible for certain cost reductions.
b) The doctor will try our best to prevent and treat because of this research may lead to harm. If the occurrence of adverse events in clinical trials, medical experts committee will identify if they are related to this research. The project team will provide treatment of the damage to the test related costs and the corresponding economic compensations.

Confidentiality

Your medical records (research case report/CRF, laboratory test results, etc.) will be kept in their entirety at the hospital where you were treated. The doctor will record your laboratory tests and other examination results in your medical record. Researchers, ethics committees and management department will be allowed access to your medical records. Any public report related to the study results will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data to the extent permitted by law.

According to the medical research ethics, in addition to personal privacy information, test data will be available to the public and sharing, query and sharing will be limited to an electronic database based on network, guaranteed not to leak any personal privacy information.

Further Information

You can ask any questions about the study and get answers at any time. If there is any important new information in the research process, which may affect your willingness to continue to participate in the study, your doctor will inform you.

Voluntary Participation and Withdrawal

Participation is entirely voluntary. You can refuse to participate or withdraw at any time without affecting your relationship with your doctor or your medical care. For your benefit, the study doctor or investigator may withdraw you from the study at any time. If you withdraw, you may be asked about your use of the study drug and may be asked to undergo a physical examination and laboratory tests for your health benefit. If your condition changes, you can seek other treatments at any time.

What to do now

Whether to participate in this study is decided by yourself (and your family). Ask your doctor any questions before making a decision. Thank you for reading the above materials. If you decide to participate in this study, please tell your doctor and he/she will arrange everything for you regarding the study. Please keep this information for your records.

Informed consent (Agree with signature page)

Project name: Efficacy and Safety of Prophylactic Treatment for Pneumocystis Jirovecii Pneumonia (PJP) in Patients with Autoimmune Inflammatory Rheumatic Disease (AIIRD)

Sponsoring institution: Department of Rheumatology and Immunology, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Statement of Agreement

I have read the above study information and had the opportunity to discuss it with my doctor and ask questions. All my questions have been satisfactorily answered.

I understand the risks and benefits of participating in this study. I know that participation is voluntary and confirm I have had sufficient time to consider it. I understand:

- I can ask my doctor for more information at any time.
- I can withdraw from the study at any time without discrimination or loss of medical care.
- The Ethics Committee or regulatory authorities may review my study records.
- I will be provided with a signed and dated copy of my informed consent.

Finally, I agree to participate in this study and will do my best to follow medical advice.

The subjects' signature: _____ Year, month, and date

Contact phone number: _____

I confirmed that the details of the trial, including its rights and possible benefits and risks, were explained to the patient and that I gave him/her a copy of a signed informed consent.

Investigator's signature: _____ Year, month, and date

Contact phone number: _____