



Patient Information Sheet

Study title

The Use of IVIG in combination with Rituximab vs Rituximab as the First line treatment of Pemphigus

Background:

Pemphigus is a rare acquired autoimmune disease in which auto-antibodies attack skin and mucosal cells producing blisters or erosions. It can be painful and relapsing even after initial remission. Most importantly, it is potentially fatal. The average mortality was about 75% before the use of systemic steroid in the 1950s.

Traditionally, treatment of pemphigus includes high dose systemic corticosteroids with or without adjuvant immunosuppressant. However, prolonged use of high dose steroids carries significant side effects including hypertension, diabetes, osteoporosis, weight gain, infection etc.

Recent clinical trials have proven Rituximab, a monoclonal anti-CD20 antibody against B-lymphocytes, as an effective treatment for patients with pemphigus. Patients treated with early use of rituximab and low dose prednisolone achieved complete remission, with less adverse events when compared to prednisolone-alone group.

Moreover, combination treatment with intravenous immunoglobulins (IVIG) and rituximab has shown to be effective for refractory cases and can potentially induce long-term complete remission after treatment, and less risks of infection.

Objective:

In this study, we aim to evaluate the efficacy and safety of early use of rituximab with or without IVIG in patients with moderate to severe pemphigus. We will also calculate the cost and risk-benefits of both treatment arms and its impact on health care economics.

This is a prospective, open-labelled randomized controlled trial.

Information about study medication:

1. Rituximab:

This medication is given intravenously and has been approved and used in severe rheumatic arthritis and B-cell lymphoproliferative disease for disease control. Although it is recommended as first line treatment in pemphigus according to the British Association of Dermatologist (BAD) 2017 guideline, currently in Hong Kong, it is used as an off-label indication in the treatment of pemphigus.

2. Intravenous immunoglobulin (IVIG):

This medication is given intravenously. It is a kind of blood product and has been used to treat multiple diseases including autoimmune neurological diseases (e.g.,

myasthenia gravis, Guillian-Barré syndrome), haematological disease (e.g., autoimmune haemolytic anaemia, immune neutropenia), and severe cutaneous adverse drug reactions (e.g., Stevens-Johnson Syndrome). According to BAD guidelines, IVIG is recommended for use in severe/ refractory pemphigus vulgaris, when first or second line treatments have failed.

Participation in the study:

If you choose to participate in the study, your study doctor will first assess your eligibility. If you are eligible, ample time would be given to read this consent form before you sign. Then you will be randomized to either arm of the treatment regime according to the study protocol. We will involve approximately 10 subjects in each arm and each would be randomised in a 1:1 ratio.

You will be monitored regularly during treatment, including blood test and chest X-ray. If you are already on systemic steroids and/or immunosuppressants, your study doctor will gradually adjust your medications as indicated and start the study drug regime for you.

During the treatment period, you will stay in the hospital to receive treatment. You may expect to see improvement, or worsening of disease, which can be a reflection of the autoimmune nature of pemphigus, as well as possible side effects of the medication used. Your study doctor, therefore, may adjust the treatment for you according to the clinical condition. If severe infection or any Serious Adverse Events happened, your study doctor will also amend your treatment and the trial may be terminated. You or your legally acceptable representative would be fully informed if information becomes available that may be relevant to your willingness to continue participation in the trial. During your participation of the study, you can contact the research team with the contact information provided below.

Study procedures:

You will be reviewed by a clinician prior to study commencement, and a skin biopsy, blood and urine tests, and chest radiograph will be done. Clinical photographs would be taken during scheduled visits and would only be used for research and clinical evaluation only. Based on the results, the clinician will assess your condition to see if you are eligible for the study. If you agree to participate in the study, you will be randomized into either arm of the study: rituximab alone or rituximab and IVIG in a 1:1 ratio.

The medications rituximab and IVIG are given intravenously, so prior to starting the medication, you will be hospitalized in Queen Mary Hospital. Blood tests will be taken prior to administration of the medication, and an intravenous cannula will be set in the vein (usually the arms) for pre-medication infusions, and drug administration. You will be monitored during the administration of the medication, and discharged after overnight observation if stable. Follow-up will take place in the dermatology outpatient clinic, usually at monthly interval, where your skin and overall condition will be reviewed, and blood tests will be taken.

Depending on which study arm you are randomized to, the frequency of drug administration is different. Both arms will complete treatment at 18 months, and you will be followed-up for at least 4 years.

Possible side effects:

In general, regarding possible common side-effects of rituximab and intravenous immunoglobulin (IVIG), patients may have the following adverse reactions:

- 1) Infusion related reaction: fever, chills/rigor, injection site pain, nausea/vomiting, headache, myalgia, dizziness, skin rash

- 2) Possible changes in cell count, neutropenia and risks of infection (including pneumocystic pneumonia, pneumonia, herpes and cytomegalovirus infections, and systemic infections).

Rare/severe reactions include renal failure especially in elderly, diabetes and pre-existing renal dysfunction, risk of thrombotic events such as previous stroke, heart attack, unpredicted transmission of blood-borne agents, severe drug reaction, anaphylaxis, shortness of breath, hypotension, and possible death. For any enquires, you can ask your study doctor anytime.

Risks of the study

- Blood tests and intravenous cannulation may cause pain, bruising, and risks of infection
- Infusion-related adverse effects: including fever, chill/rigors, injection site pain, nausea and vomiting, aesthesia, headache, myalgia, giddiness, rhinitis, throat irritation, pruritus, skin rash, anaphylactic reaction, arterial and venous thrombosis
- Risks of infection: including urinary tract infections, pneumonia, pneumocystic pneumonia, herpes simplex, herpes zoster, cytomegalovirus infection, and pyelonephritis. Lung, and brain abscess. Severe hypogammaglobulinaemia, and high-dose immunosuppressants may be possible risk factors for systemic infections
- Haemolytic anaemia
- Toxic epidermal necrolysis
- Parkinsonism
- Acute meningitis syndrome
- Acute renal failure
- Transmission of blood-borne agents such as hepatitis B/C and HIV for IVIG group

Liability & payment:

This study is performed under the Department of Medicine, Queen Mary Hospital, The University of Hong Kong. This study is partially funded by the Chau Hoi Shuen Foundation. There is no legal liability to neither parties nor Hospital Authority in relationship to this study.

You will receive no payment or compensation from the study participation. You do not need to pay for the study medication but you will pay the consultation /admission fee and concomitant medications as usual and would be required to adhere to the treatment plan.

This study has been reviewed and approved by Department of Health and Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB).

Benefits

No financial compensation or reimbursement for participation in this study will be given.

Your medical care will be continued as usual and receive long-term remission in the clinic of Queen Mary Hospital.

The results might be published in medical literature. You may ask your doctor for details of the results.

Alternatives to Taking Part in the Study

You can choose not to participate in the study. Alternatives to taking part in the study include conventional therapy for pemphigus, which include oral steroids, and other oral immunosuppressive therapy such as azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, and plasmapheresis, and you can also choose Rituximab as your self-financed medical treatment for pemphigus. For details of self-financed rituximab treatment plan, please discuss with your doctors.

Withdrawal from the study

Participation in this study is completely voluntary. You can choose to withdraw from the study at any time without consequence or affect your disease management. You are assured that refusal or early discontinuation of participation in the study will not result in any loss of benefits or penalty to a patient's care. Your doctor will continue to assess your condition and give you appropriate treatment as indicated.

For safety and efficacy assessments, if you prematurely discontinue study drug, you should continue to be followed up for all scheduled visits, and blood tests (unless you have decided to discontinue the study participation entirely).

Confidentiality and Patient Rights:

Under the laws of Hong Kong (in particular the Personal Data (Privacy) Ordinance, Cap 486), you enjoy or may enjoy rights for the protection of the confidentiality of your personal data, such as those regarding the collection, custody, retention, management, control, use (including analysis or comparison), transfer in or out of Hong Kong, non-disclosure, erasure and/or in any way dealing with or disposing of any of your personal data in or for this study. For any query, you should consult the Privacy Commissioner for Personal Data or his office (Tel No. 2827 2827) as to the proper monitoring or supervision of your personal data protection so that your full awareness and understanding of the significance of compliance with the law governing privacy data is assured.

By consenting to participate in this study, you expressly authorize:

- The Principal Investigator and his research team and the ethics committee (Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster) responsible for overseeing this study to get access to, to use, and to retain your personal data for the purposes and in the manner described in this informed consent process; and
- The relevant government agencies (e.g., the Hong Kong Department of Health) to get access to your personal data for the purposes of checking and verifying the integrity of study data and assessing compliance with the study protocol and relevant requirements.

All data will be stored in a database with limited access for 15 years.

Your data will be kept strictly confidential and will only be assessed by a designated adjudication committee. You can contact our investigator (Tel: Miss Sham 2255 6489, email: js83213@hku.hk) for questions related to the present study. You can also contact Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster at 2255 4086 for patient right-related questions.



Patient Informed Consent

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By signing this consent, I, _____, hereby agree to participate in the captioned study and I fully understand my disease condition and treatment options, indication and possible side-effect of the medication. I have read and understood the information sheet for the above study and have had the opportunity to ask questions. **I confirm that this consent form has been explained to me in terms which I understand.**

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I also understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I also give permission for the data collection related to the study, **including medical photographs to be made of me, I understand that the images will be used in medical publications and presentation without identifying information.** All data collected will be kept confidential and used solely for this study analysis.

Name of Patient: _____

Signature of Patient: _____

Date: _____

Name of Witness: _____

Signature of Witness: _____

Date: _____

Name of Investigator: _____

Signature of Investigator: _____

Date: _____