

A Study of Eltrombopag and Recombinant Human Thrombopoietin In Primary Immune Thrombocytopenia

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PROTOCOL SUMMARY

Title of trial	A prospective and retrospective observational study of switching eltrombopag and rh-TPO in Chinese adult patients with primary immune thrombocytopenia
Participants	Peking University People's hospital, Institute of Hematology
Background	<p>Immune thrombocytopenia (ITP), an autoimmune disorder characterized by thrombocytopenia due to platelet destruction and impaired platelet production, is responsible for various degrees of bleeding signs ^{1, 2}. The pathogenesis of ITP includes immune-mediated clearance of antibody-coated platelets by macrophages, together with antibody-mediated megakaryocyte apoptosis and the suppression of thrombopoiesis activities ^{3, 4}. Primary ITP is defined as isolated thrombocytopenia with platelet counts $<100*10^9/L$ after the exclusion of all other conditions that lead to thrombocytopenia ^{2, 4, 5}.</p> <p>ITP is a highly heterogeneous disorder in adults with symptoms ranging from mild bruising to intracranial hemorrhage ^{4, 6}. The goal of treatment is to achieve a platelet count adequate to prevent bleeding while minimizing treatment-related toxicity ^{2, 6}. When platelet counts fall below $30*10^9/L$, treatment is considered as the patient suffers from increasing risk of fatal bleeding ². Corticosteroids (high-dose dexamethasone or prednisone) with or without intravenous immunoglobulin (IVIg) are the first-line treatment strategies to decrease autoantibody-mediated platelet destruction, increase platelet production, and reduce bleeding ^{5, 7}. For most adult patients, however, relapse occurs upon cessation of steroid treatment; as a result, second-line therapies are considered to maintain a sustained increase in the platelet count while minimizing adverse events to allow for the possibility of attaining a remission (defined as a platelet count $\geq30*10^9/L$ in the absence of any ITP-specific treatment) ⁸.</p> <p>Thrombopoietin receptor agonists (TPO-RAs) represent a highly effective and well-tolerated second-line ITP treatment that provides excellent responses ($>60\%$) in splenectomized and nonsplenectomized ITP patients (Grade A recommendation, evidence level Ib) ^{5, 8}. In China, rh-TPO and eltrombopag are the two distinct TPO-RAs widely used in clinical practice. Rh-TPO is a TPO peptide mimetic that is injected subcutaneously, whereas eltrombopag is a TPO nonpeptide mimetic administered orally ^{1, 3, 9}. Rh-TPO, composed of two IgG1 constant regions (Fc fragments) linked to a peptide domain containing four binding sites for the thrombopoietin receptor (TPO-R), activates TPO-R by binding to the extramembrane domain like endogenous TPO ^{1, 10}. Eltrombopag is a 442-Da drug that binds to the transmembrane domain of TPO-R and activates it ^{1, 10}. There is a local rh-TPO launched in China 7 years ahead of eltrombopag, which used to dominate the market. Both drugs are recommended by the latest Chinese guideline as second-line or emergent therapy for treatment of adult primary immune thrombocytopenia ⁷.</p>

Study Rationale	<p>According to the findings of mechanism-based studies, rhTPO competes with endogenous TPO for binding to TPO-R while eltrombopag has an additive effect with endogenous TPO¹⁰, indicating that the treatment mechanism and side-effect profiles could be somewhat different between these drugs^{9, 10}. Therefore, when there's a lack of response or when adverse events become a problem with one TPO-RA, switching to another TPO-RA provides useful information for the management of adult ITP patients^{8, 9}.</p> <p>Khellaf et al. retrospectively reviewed data of 46 ITP patients who sequentially switched from eltrombopag to romiplostim (a TPO-RA similar to rhTPO in mechanism) or vise versa due to varying reasons including lack of efficacy (n=23), platelet-count fluctuations (n=11), side effects (n=4), and patient's preference (n=8). Switching was shown effective in 50-80% of the patients, with eradication of platelet fluctuations in 54% and side effects resolved in 100%¹. Another retrospective analysis of 26 ITP patients showed that for patients who switched the TPO-RA as a result of inefficiency (n=10), switching from romiplostim to eltrombopag led to 100% response rates, whereas switching from eltrombopag to romiplostim led to 66% response rates. The response rate was 100% in patients who switched due to side effects (n=5) or patient preference (n=8)¹⁰. In a study of 51 primary ITP adult patients switching from romiplostim to eltrombopag, response rate was 80% (41/51) with efficacy maintained for a median of 5.5 (range, 2-9) months in all patients who switched because of patient preference (n = 16), platelet-count fluctuation (n = 6) and side-effects (n = 4)⁹. Cantoni et al. analyzed clinical characteristics associated with response to the switch of TPO-RAs and found that lines of previous therapy, as well as disease duration would lower the probability to respond. According to the study, response was achieved/regained in 57.8% of patients who switched for efficacy issues and 80% who switched for non-efficacy issues; once response to the 2nd TPO-RA is achieved, it is possible to maintain long-term effect in these patients³.</p> <p>Based on the clinical evidence, it is shown that switching from one TPO-RA to another, as well as sequential therapy, provides favorable outcomes of response and tolerability (evidence levels IIb, III)⁸. However, current studies almost exclusively focus on the effect of switching between romiplostim and eltrombopag; whether there is also absence of cross-resistance between rhTPO and eltrombopag remains to be investigated. In addition, clinical evidence on TPO-RA switching is proposed on the basis of retrospective studies. Therefore, we propose here an observational study with retrospective and prospective design to evaluate the response and safety profiles of switching between eltrombopag and rh-TPO in Chinese adult ITP patients; the preference of patients and doctors will also be assessed in this study.</p>
Objectives	<p><u>Primary Objective:</u></p> <p>To assess the response on one TPO-RA after switching from another.</p> <p><u>Secondary Objectives:</u></p> <p>To assess the patterns of response and switching.</p>

	<p>To understand the preference of patients and doctors.</p> <p>To study the safety profiles associated with rhTPO and eltrombopag after switching.</p> <p><u>Exploratory Objectives:</u></p> <p>To analyze the associations between clinical characteristics and response after switching.</p> <p>To explore the effect of rescue medication on response after TPO-RA switching.</p>
Endpoints	<p>Primary endpoint:</p> <ul style="list-style-type: none"> ➤ Rate of response at 6 weeks after switching from rhTPO to eltrombopag or vice versa <p>Response is defined according to the Chinese guidelines for treatment of adult primary immune thrombocytopenia as ⁷:</p> <p>Complete response (CR): platelet count $\geq 100 \times 10^9/L$ and absence of bleeding.</p> <p>Response (R): platelet count range $30-100 \times 10^9/L$, at least doubling of the baseline count, and absence of bleeding.</p> <p>No response (NR): platelet count $< 30 \times 10^9/L$, or less than doubling of the baseline count, or bleeding.</p> <p>The rate of response at 6 weeks includes the total proportion of patients who achieved CR and R at 6 weeks in the groups switch from rhTPO to eltrombopag and eltrombopag to rhTPO, respectively.</p> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> ➤ Rate of response at 6 weeks after switching, according to the reasons of switching <p>The reasons of switching include ³:</p> <p>Lack of efficacy:</p> <ul style="list-style-type: none"> -1st TPO-RA failure: no response to either one TPO-RA administered before switch -Loss of response: relapsed after transient response to 1st TPO-RA (relapse is defined as platelet count $< 30 \times 10^9/L$, or less than doubling of the baseline count, or bleeding, after the achievement of CR or R. The blood platelet count should be confirmed on at least two separate occasions, which is at least 1 day apart when used to define relapse ⁷) <p>Platelet count fluctuations: unstable platelet counts necessitating rescue therapy or transient TPO-RA dose modifications/withdrawal with associated risk of either rebound thrombocytopenia/bleeding or thrombocytosis</p> <p>Patient's preference</p> <p>Development of adverse events necessitating 1st TPO-RA discontinuation</p> <ul style="list-style-type: none"> ➤ Proportion of patients who achieved, regained, and maintained response at 6 weeks after switching <p>Response achieved refers to patients who failed the 1st TPO-RA achieve CR or R at 6 weeks after switching.</p> <p>Response regained refers to patients who lost response to the 1st TPO-RA achieve</p>

CR or R at 6 weeks after switching.

Response maintained refers to patients who achieved CR or R with the 1st TPO-RA and still respond to the 2nd TPO-RA at 6 weeks after switching.

- Rate of response at 3 months after switching from rhTPO to eltrombopag or vice versa
- Rate of response at 3 months after switching, according to the reasons of switching
- Proportion of patients who achieved, regained, and maintained response at 3 months after switching
- Time to response from 1st TPO-RA switching for patients who switch due to lack of efficacy
- Duration of response from 1st TPO-RA switching for patients who switch due to lack of efficacy

Duration of response is defined as the time from when CR or R is achieved/regained to the time of relapse.

- Proportion of patients with any bleeding (WHO bleeding scale grade 1–4¹¹) and clinically significant bleeding (WHO bleeding scale grade 2–4¹¹)
- Total score of bleeding calculated according to the Bleeding Rating System⁷
- Patient and physician's treatment preference

At 6 weeks after switching, patients will be asked whether they prefer to continue treatment with rhTPO or eltrombopag, or whether they had no preference¹². In addition, patients who prefer one TPO-RA over the other will be queried on the reasons of preference (Patient preference questionnaire attached as Appendix 1).

At 6 weeks after switching, physicians will also be asked whether they prefer to further treat the patient with rhTPO or eltrombopag, or whether they had no preference, taking into account the patient's preference, response, and tolerability¹².

At 3 months after switching, the measurement will be applied again.

- Safety of treatment

The safety of treatment will be determined from adverse events summarized by incidence and severity, and from clinical laboratory evaluations, physical examinations and ophthalmological examinations carried out during scheduled study visits.

Exploratory endpoints:

- Association between clinical characteristics and response after switching

The following clinical characteristics will be compared between responders and non-responders at 6 weeks and 3-month after switching, respectively: gender (male vs female), age at 1st TPO-RA, time from diagnosis to 1st TPO-RA, lines of previous therapy before 1st TPO-RA, maximum 1st TPO-RA dose received vs. not received, splenectomy status (yes vs no), switch sequence (rhTPO to eltrombopag or vice versa), switching behavior, switch due to efficacy vs non-efficacy issues, and 1st TPO-RA failure vs loss of response.

	<ul style="list-style-type: none"> ➤ The effect of rescue medication on response after TPO-RA switching. Clinically, a stable response refers to response achieved without receiving rescue treatment¹. Additional analysis will be conducted to explore the influence of rescue medication on response after switching from rhTPO to eltrombopag or vice versa.
Trial Design	<p>This is a prospective and retrospective observational study of switching eltrombopag and rh-TPO in Chinese adult patients with primary immune thrombocytopenia. A schematic illustration of the study design is shown as follows:</p> <div style="text-align: center; margin: 20px 0;"> </div> <p>The study includes two stages: the retrospective stage and the prospective stage. Primary ITP patients who failed initial glucocorticosteroid treatment and receive rh-TPO and then switch to eltrombopag or vice versa will be screened for eligibility. Medical records will be retrospectively reviewed to collect baseline data before 1st TPO-RA administration, information on the 1st TPO-RA, as well as the reason for switch. Patients who meet the eligibility criteria upon medical history review and clinical evaluation will be enrolled at the time of switch. The switch procedure is as per physician preference and clinical practice.</p> <p>After enrollment, patients will be followed up prospectively on administering the 2nd TPO-RA. Both rh-TPO and eltrombopag are applied according to the approved label and clinical practice, in considering the actual condition of a patient. For patients who switch from rhTPO to eltrombopag, platelet counts will be obtained weekly under stable dose and monthly following establishment of a stable platelet count ($\geq 50*10^9/L$ for at least 4 weeks), while platelet counts will be obtained at least once a week during dose adjustment. Liver function tests (ALT, AST, TB) will be performed monthly under stable dose but increased to bi-weekly during dose adjustment. For patients who switch from eltrombopag to rhTPO, platelet counts will be obtained every other day during initial treatment and weekly during maintenance therapy.</p> <p>Platelet counts will be obtained at least once a week for all patients who suspend/stop their 2nd TPO-RA, while liver function tests will be performed bi-weekly in patients who suspend/stop eltrombopag as their 2nd TPO-RA. Once treatment is resumed, monitoring of platelet counts and liver function will be performed as per during treatment administration. An end-of-study visit will be performed for all patients at</p>

	<p>3 months after switching.</p> <p>The observation period is 3-month for each patient enrolled. Response to 2nd TPO-RA will be assessed throughout the observation period with response at 6 weeks being the primary evaluation. Adverse events, including bleeding events, will be assessed and recorded together with concomitant ITP treatment. Preference of patients and doctors on the two TPO-RAs will also be assessed.</p>
Investigational Drug Administration	<p>Patients will initiate eltrombopag treatment with a dose of 50 mg once daily. Dose adjustment of study medication will be allowed to maintain platelet counts between 50*10⁹/L and 250*10⁹/L.</p> <p>Patients will initiate rh-TPO with a dose of 300 U/kg/d for \leq14d. Patients who attained stable PLT counts (\geq50*10⁹/L) in two consecutive tests will enter maintenance therapy, starting with every other day administration of rhTPO, then adjust dose interval to maintain platelet counts at 30-100*10⁹/L.</p>
Dose Adjustment Guidelines	<p>The following information serves as a reference; actual dose adjustment will be conducted according to clinical practice in considering the medical condition of a patient:</p> <p>Eltrombopag: refer to Table 2.</p> <p>RhTPO:</p> <p>At initial treatment, rhTPO will be suspended when platelet counts \geq100*10⁹/L. During maintenance therapy, patients with platelet counts $>$150*10⁹/L will suspend treatment until platelet counts drop to \leq150*10⁹/L. Dosing interval will be prolonged when platelet count is \geq100*10⁹/L to \leq150*10⁹/L. Dose modification is not required when platelet count is \geq30*10⁹/L to $<$100*10⁹/L¹³.</p>
Patient Population	Chinese adult patients with primary immune thrombocytopenia who failed first-line corticosteroid therapy and received rhTPO and then switch to eltrombopag or vice versa.
Key Inclusion Criteria	<ul style="list-style-type: none"> • Age 18 years or older • Chinese ethnicity • Primary ITP diagnosed according to the current definitions ^{7, 8, 14, 15} • Failed initial glucocorticosteroid treatment, • Applying rhTPO or Eltrombopag as subsequent treatment • Switch from rh-TPO to eltrombopag or vice versa • Treatment on rhTPO for 14 days minimum or Eltrombopag for 4 weeks minimum, if the reason of switching is lack of efficacy or platelet count fluctuations • Available follow-up at least 6 weeks after switching

Key Exclusion Criteria	<ul style="list-style-type: none"> • HIV positive status, or active infection of HBV or HCV • Suffering from a serious or progressive disease, which, in the investigator's judgment, put the subject at undue risk for participation in this study (i.e. cancer or pre-cancer, immunocompromised, uncontrolled diabetes, epilepsy, severe cardio-cerebrovascular disease(s) (i.e. stroke, idiopathic aortic stenosis, aneurysm, hypertrophic obstructive cardiomyopathy, ischaemic heart disease, tachyarrhythmias, severe heart failure [classified as NYHA III-IV], severe lung dysfunctions, etc)) • History of thrombosis plus two or more risk factors as defined in Caprini thrombosis risk assessment model ¹⁶ • Lactating or pregnant women, or WOCBP who are unwilling to use highly effective contraceptive measures during the study period • Abnormal liver and renal functions: AST or ALT or total bilirubin $\geq 1.5 \times$ ULN, and/or creatinine $\geq 176.8 \mu\text{mol/L}$ • Women of childbearing potential (WOCBP) that are pregnant or wish to become pregnant during the prospective phase of the study. • Other conditions which the investigator considers inappropriate for enrollment
Safety Monitoring and Reporting	<p>Adverse events (AEs) will be collected throughout the study period and classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0</p> <p>(https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)</p> <p>Also, whether an AE fulfills the criteria of a SAE will be judged according to the definition of ICH-E2. All SAEs occur during the study period will be reported to the Sponsor's Pharmacovigilance contact within 24 hours upon knowledge of the investigator. The following information is the minimum requirement of reporting:</p> <ul style="list-style-type: none"> • Patient identifier • Product name • SAE description including assessment of causal relationship and severity • Investigator name and contact details <p>Women who become pregnant during the study have to immediately inform their physician and discontinue, as neither rhTPO nor Eltrombopag currently have sufficient data to inform a drug-associated risk of adverse developmental outcomes.</p>
Sample Size Justification	<p>Total Planned Number of Patients: 100 patients (~50 patients in each switch sequence but not a strict 1:1 ratio)</p> <p>➤ The purpose of this study is not to compare the efficacy differences between the two switch groups but to describe the rate of response, so the sample size cannot be calculated.</p>

	<p>Sample size rationale:</p> <ul style="list-style-type: none"> ➤ According to a published similar literature, it is estimated that about 100 patients can reveal a certain proportion of efficacy ³; ➤ Using the cross-sectional sampling method, the estimated response rate of these two drugs is ~70% (95% CI, 50%-90%), the sample size would be 80. So, 100 patients' size was decided taking the 20% drop-out rate into consideration. ➤ According to our previous study, it is expected to complete the observation of 100 patients within one and a half year.
Statistical Analysis	<p>Statistical analysis methods:</p> <p>Statistical analysis will be conducted by SAS Version 9.2 or above. Descriptive statistics for continuous variables include minimum, maximum, mean ± standard deviation and median with inter-quartile ranges (IQR). Categorical variables will be described as frequencies and percentages. Percentage will be calculated based on non-missing data unless otherwise specified. Comparison between categorical variables will be performed using chi-square test or Fisher's exact test, while comparison between continuous variables will be performed using two-sample t test for parametric data and Wilcoxon rank sum test for non-parametric data. Logistic regression will be used to assess the association between clinical characteristics and outcome of response. Time-to-event data will be described by Kaplan-Meier survival curve with log-rank test for between-group comparison.</p> <p>Unless specified, statistical testing will be carried out bilaterally with significance level alpha=0.05, i.e. a p-value of less than or equal to 0.05 will be considered as statistically significant. Methods of descriptive analysis and hypothesis testing will be selected according to the data characteristics. Transformations will be undertaken as needed.</p> <p>Analysis sets:</p> <p>Full Analysis Set (FAS): includes all patients who receive at least one dose of the 2nd TPO-RA and have response assessed at 6 weeks after switching</p> <p>Safety Set (SS): includes all patients who receive at least one dose of the 2nd TPO-RA after switching.</p> <p>Efficacy analysis will be conducted on FAS and safety analysis on SS.</p>

Table 1 Time and Events

Study procedures	Screening	During Treatment				Safety follow-up after treatment suspension/stop	End-of-study Visit
Visit schedule	-14~1d	Every week \pm 3d	Every 2 weeks	Every 4 weeks	Every 8 weeks	Every week \pm 3d	12 weeks \pm 7d

			±3d	±4d	±4d		
Written informed consent	X						
Demographics	X						
Medical history	X						
Physical examination	X	X				X	X
Ophthalmologic examination	X						X
CBC (incl. platelet count)	X	X ^{a, b}		X ^b		X ^e	X
Peripheral blood smear	X						
Liver function tests (ALT, AST, TB)	X		X ^c	X ^c		X ^d	X
Other clinical chemistry (incl. Cr)	X						X
Coagulation tests	X				X		X
Thyroid function test	X						
HBV, HCV, HIV testing	X						
ECG	X						
Ultrasound (spleen)	X				X		X
Chest X-ray	X						
Bleeding assessment	X	X				X	X
Bone marrow aspirate	As clinically required.						
Pregnancy test	X						X
Concomitant therapy ^f	X	X				X	X
AE/SAE assessment	X	X				X	X

- a. For patients who switch from eltrombopag to rhTPO, CBC should be performed every other day during initial treatment and weekly during maintenance therapy.
- b. For patients who switch from rhTPO to eltrombopag, CBC should be monitored weekly until stable platelet count is observed ($\geq 50*10^9/L$ for at least 4 weeks), then CBC will be monitored every 4 weeks. Platelet counts will be obtained at least once a week during dose adjustment.
- c. For patients who switch from rhTPO to eltrombopag, liver function tests (ALT, AST, TB) will be performed every 4 weeks under stable dose but increased to every 2 weeks during dose adjustment.
- d. For patients who switch from rhTPO to eltrombopag, liver function tests (ALT, AST, TB) will be performed every 2 weeks after treatment suspension/stop.
- e. The frequency of platelet monitoring can be increased to twice weekly for patients who suspend/stop eltrombopag due to platelet counts $>250*10^9/L$.
- f. Record concomitant ITP treatment (including rescue medications), anticoagulants, and NSAIDs.

Table 2 Dose Adjustment Guidelines of Eltrombopag

After initiating eltrombopag, the dose should be adjusted to achieve and maintain a platelet count $\geq 50*10^9/L$ as necessary to reduce the risk of bleeding. A daily dose of 75 mg must not be exceeded.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in **Table 2**.

During therapy with eltrombopag, platelet counts should be assessed weekly until a stable platelet count ($\geq 50*10^9/L$ for at least 4 weeks) has been achieved. Platelet counts should be obtained monthly thereafter.

Platelet count	Dosage adjustment or response
$<50*10^9/L$ following at least 2 weeks of therapy	Increase daily dose as per 25mg. Monitor platelet count at least once a week, wait for 2 weeks, assess the treatment effect after dose increase, and consider whether further dose adjustment is needed. Maximum daily dose is 75mg per day.
$\geq 50*10^9/L$ to $\leq 150*10^9/L$	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
$>150*10^9/L$ to $\leq 250*10^9/L$ *	Decrease daily dose as per 25mg. Monitor platelet count at least once a week, wait for 2 weeks, assess the treatment effect after dose decrease, and consider whether further dose adjustment is needed.
$>250*10^9/L$ **	Suspend eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is $\leq 100*10^9/L$, reinitiate therapy at a daily dose reduced by 25 mg **. The standard dose adjustment, regardless of increase or decrease the dose, is per 25mg qd. Following any dose adjustment, platelet count should be monitored at least once a week for 2-3 weeks. After waiting for at least 2 weeks, observe the effect of dose adjustment on platelet count, and then consider whether to continue to adjust the dose. Any patient with cirrhosis (i.e. child Pugh score ≥ 5) will wait for 3 weeks before increasing the dose.

Notes:

* For patients with platelet counts $>150*10^9/L$ during any time point of treatment, decrease the dose to subsequent lower dose (for example, decrease 75mg qd to 50mg qd, or decrease 75mg qd to 75mg qd and 50mg qd in turn, etc.) or decrease the dosing frequency (for example, decrease 25mg qd to 25mg qod, or consecutive 2 days for medication of 25mg qd and 1 day without the medication, or consecutive 3 days for medication of 25mg qd and 1 day without the medication, etc.).

**Once platelet count is $\leq 100*10^9/L$, restart the treatment but decrease to subsequent lower dose (for example, decrease 75mg qd to 50mg qd, or decrease 75mg qd to 75mg qd and 50mg qd in turn, etc.) or decrease the dosing frequency (for example, decrease 25mg qd to 25mg qod, or consecutive 2 days for medication of 25mg qd and 1 day without the medication, or consecutive 3 days for medication of 25mg qd and 1 day without the medication, etc.).

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Informed Consent Form

A Study of Eltrombopag and Recombinant Human Thrombopoietin In Primary Immune Thrombocytopenia

Dear subjects:

We are going to carry out a prospective clinical study on the conversion between eltrombopag and recombinant human thrombopoietin (rhTPO) in the treatment of drug-resistant / relapsed primary ITP. As you have immune thrombocytopenia and will be treated with eltrombopag or rhTPO, and your specific conditions meet the inclusion criteria of the study, we would like to invite you to participate in this study.

This informed consent will introduce you to the purpose, steps, benefits, risks and inconvenience of this study, as well as your rights and interests. Please carefully read it and make a decision on whether to participate in the study. When the researcher explains and discusses the informed consent form to you, you can ask questions at any time and ask him / her to explain to you what you don't understand. You can discuss with your family, friends and your doctor before making a decision.

If you are currently participating in other clinical studies, please inform your doctor or researcher.

The project leader of this study is Professor Zhang Xiao-hui, Peking University People's Hospital, Peking University Institute of Hematology, Beijing, China.

1. Why do we do this research?

ITP is an autoimmune disease, which is one of the most common hemorrhagic diseases that seriously endanger human health. Glucocorticoid and intravenous immunoglobulin are recommended as the first-line treatment for ITP patients. However, more than 30% of ITP patients have poor response to glucocorticoid treatment, and 50-85% of patients with effective corticosteroid therapy still relapse in the first year of treatment. In addition, long-term use of glucocorticoid treatment of patients with serious side effects, can lead to diabetes, hypertension, serious systemic infection and necrosis of the femoral head and other serious complications. Therefore, in-depth study of new treatment plan is an important clinical and scientific problem to be solved in this field.

Thrombopoietin (TPO) is the most important cytokine regulating megakaryocyte development and platelet production, which can promote the differentiation of megakaryocytes and the production of platelets. Studies have shown that the plasma TPO level is not increased or slightly increased in ITP patients, and megakaryocytes in bone marrow of ITP patients are increased or accompanied with maturation disorder. The relative deficiency of endogenous TPO production is one of the causes of thrombocytopenia, which provides a basis for the treatment of ITP with TPO and its receptor agonists. Many thrombopoietins (rhTPO, eltrombopag, romiplostim) have been recommended for second-line treatment of adult ITP.

RhTPO, similar to endogenous TPO, has the effect of increasing platelets. The efficacy of rhTPO in the treatment of chronic, refractory and severe ITP has been confirmed. RhTPO has fewer adverse reactions, including occasional fever, chills, general discomfort, fatigue, muscle soreness, headache, dizziness and high blood pressure, which generally does not need to be addressed and can recover by itself.

Eltrombopag is a TPO receptor agonist, which has been approved by FDA for the treatment of thrombocytopenia in patients with chronic ITP and poor response to corticosteroids, immunoglobulin or splenectomy. The common side effects of eltrombopag include nausea, vomiting, menorrhagia, muscle pain, paresthesia, cataract, dyspepsia, liver and kidney dysfunction, ecchymosis, thrombocytopenia and conjunctival hemorrhage.

There are many differences between the effect of eltrombopag and that of rhTPO and romiplostim. First of all, although the two molecules are bound to the same receptor, they are bound to different sites. Eltrombopag does not compete with TPO to bind to the distal cytokine homologous region of TPO receptor. Whether in vitro or in vivo, the effect of eltrombopag is additive to that of TPO. Secondly, the activation of JAK and STAT pathway by eltrombopag is different from that of TPO. Different from rhTPO, the Akt pathway was not activated by eltrombopag after binding to TPO receptor.

It has been confirmed in many retrospective studies that there is no cross resistance between eltrombopag and romiplostim. However, whether there is cross resistance between eltrombopag and rhTPO in clinical application, and whether their side effects overlap, especially for

glucocorticoid resistant / recurrent ITP, has not been reported.

To sum up, our research group believes that the mechanism of action of eltrombopag and rhTPO is different, forming this study: To observe the safety and efficacy of eltrombopag in ITP patients, who are ineffective or intolerable to the treatment of rhTPO; to observe the safety and efficacy of rhTPO in ITP patients, who are ineffective or intolerable to the treatment of eltrombopag.

2. Who will be invited to participate in the study?

Adult ITP patients who have been confirmed to be resistant or relapsed after full dose corticosteroid therapy and currently use only one of the two drugs of eltrombopag or rhTPO and need to be replaced with another one.

3. How many people will participate in this study?

100 subjects.

4. How will the study be conducted?

Patients with glucocorticoid resistant / relapsed ITP who are currently using eltrombopag and need to be replaced with rhTPO for various reasons, or who are currently using rhTPO and need to change to eltrombopag for various reasons were included in the study. Physical examination and relevant laboratory tests were completed and informed consent was signed. The treatment was completed according to the clinical treatment plan, and the follow-up period was 1 year. Platelet count, adverse reactions and other indicators were followed up every week in the first three months of treatment, then once every two weeks until six months, and then once a month until one year.

5. How long will this study last?

Each patient will be followed up for 1 year.

6. What are the risks of participating in this study?

This study only collects clinical data and information, which is an observational study and does not bring the risk of examination and treatment to the subjects.

7. What are the benefits of participating in this study?

Your participation in this study will not bring immediate benefits, but your participation will help to clarify the development of your disease; we hope that the information from your participation in this study will benefit you and other patients with the same condition in the future.

8. Is it necessary to participate in and complete the study?

Whether you participate in this study is entirely voluntary. If you don't want to, you can refuse to participate. This will not have any negative impact on your current or future medical treatment. The doctor will treat you according to the routine. Even if you agree to participate, you can change your mind at any time and tell the researcher to quit the study. Your withdrawal will not affect your access to normal medical services. In principle, after you quit, the researcher will keep the relevant information of you obtained until the final destruction, and will not continue to use or disclose the information during this period. During the study, we will inform you of any information that may affect your decision to continue to participate in the study.

9. What are the costs and compensation for participating in the study?

This study will only collect your relevant information during the follow-up. Your treatment plan, including medication and examination fees, should be paid by yourself.

10. Are subjects remunerated for participating in the study?

You were not paid for the study.

11. How to deal with research-related injuries?

If you are injured due to participating in this study, we hope you can inform the researcher as soon as possible, and we will provide necessary medical measures according to the clinical routine. Our institution (Peking University People's Hospital, Peking University Institute of Hematology, Beijing, China) will take necessary medical measures for the adverse reactions occurred during the study period.

12. Will my information be kept confidential?

If you decide to participate in this study, your personal data about your participation in the study are confidential. Information that identifies you will not be disclosed to members outside the research

group unless have your permission. All study members and study sponsors are required to keep your identity confidential. Your files will be kept in a locked file cabinet for researchers' reference only. If necessary, members of the government administration or medical ethics committee may access your personal data in the research unit according to regulations. When the results of this study are published, no identity information will be disclosed.

13. Who should I contact if I have any questions or difficulties?

The general director of the project is Zhang Xiao-hui, chief physician of Peking University People's Hospital (Tel: 010-88324577). If you have any questions related to this study, please contact Dr. Cai Xuan at 010-88324577.

If you have questions related to your own rights and interests, you can contact the medical ethics committee of Peking University People's Hospital at 010-88324516.

Informed consent (signature page)

Statement by the researcher

I have informed the subject of the research background, purpose, steps, risks and benefits of the prospective clinical study project of converting eltrombopag and rhTPO for drug-resistant / relapsed ITP. I have given him / her enough time to read the informed consent form, discuss with others, and answer his / her research questions; I have informed the subject that he / she can contact Dr. Zhang Xiao-hui at any time when he / she encounters any research related problems and contact the medical ethics committee of Peking University people's Hospital at any time in case of problems related to his / her own rights / interests, and provided accurate contact information; I have informed the subject that he / she can withdraw from the study without any reason; I have informed the subject that he / she will obtain a copy of this informed consent form with my / his / her signature on it.

Signature of researcher with informed consent (in italics)

Date

Signature of researcher with informed consent (handwritten)

Date

Statement by the subject

I have been informed of the background, objectives, procedures, risks and benefits of the prospective clinical study of eltrombopag and rhTPO conversion therapy for resistant / relapsed ITP. I have enough time and opportunity to ask questions, and I am satisfied with the answers. I also have been told who I should contact when I have questions, want to reflect difficulties, concerns, have suggestions for research, or want further information or help with research. I have read this informed consent form and agree to participate in this study. I know that I can withdraw from this study at any time during the study without any reason. I also have been told that I would get a copy of this informed consent form with my signature and that of the researcher.

Signature of the subject (in italics)

Date

Signature of the subject (handwritten)

Date

(Add or replace the following methods when the subjects are lack of the ability of informed consent)

Signature of legal representative (in italics)

Date

Signature of legal representative (handwritten)

Date

Relationship with the subjects

Date

Signature of the subject (if possible)

Date