Protocol Title (Scientific Title) -

"Efficacy of Eltrombopag & Prednisolone Versus Prednisolone Monotherapy in Newly Diagnosed Immune Thrombocytopenia- A Randomized Control Trial"

Brief Title-

Role of Eltrombopag as First Line Therapy in Primary Immune Thrombocytopenia.

Last Update- - 22.01.2024

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1. Title of Study:

Efficacy of Eltrombopag & Prednisolone Versus Prednisolone Monotherapy in Newly Diagnosed Immune Thrombocytopenia- A Randomized Control Trial

2. Brief Title- Role of Eltrombopag as First Line Therapy in Primary Immune Thrombocytopenia.

3. Principal Investigator(s):

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5. Place of the Study/Institution(s):

Department of hematology and BMT Unit, Dhaka Medical college hospital, Dhaka

6. Type of Study: A double blind, placebo control, Randomized Clinical Trial.

7. Duration of Study: One year

Put Tick sign (√) appropriate answers against each of the following statement
(If not Applicable, Please write NA)

1. Source of Population:			**4. Are subjects clearly informed about:**		
(a) Ill Subject	**√Yes**	**No**	(a) Nature and purpose of Study	**√Yes**	**No**
(b) Non-ill Subject	**Yes**	**√No**	(b) Procedures to be followed including alternatives used	**√Yes**	**No**
(c) Minors or persons under guardianship	**Yes**	**√No**	(c) Physical risks	**√Yes**	**No**
2. Does the study Involve:			(d) Private questions	**√Yes**	**No**
(a) Physical risks to subjects	**√Yes**	**No**	(e) Invasion of the Body	**√Yes**	**No**
(b) Social Risks	**Yes**	**√No**	(f) Benefits to be derived	**√Yes**	**No**
(c) Psychological risks to subjects	**Yes**	**√No**	(g) Rights to refuse to participate or to withdraw from study	**√Yes**	**No**
(d) Discomfort to subjects	**√Yes**	**No**	(h) Confidential handling of data	**√Yes**	**No**
(e) Invasion of the body	**√Yes**	**No**	(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure	**√Yes**	**No**
(f) Invasion of Privacy	**Yes**	**√No**	**5. Will signed consent form/verbal consent be required:**		
(g) Disclosure of information damaging to subject or others	**Yes**	**√No**	(a) From Subjects	**√Yes**	**No**
3. Does the study involve:			(b) From parent or guardian(if subjects are minors)	**Yes**	**√No**
(a) Use of records(hospital, medical, death, birth or other)	**Yes**	**√No**	6. Will precautions be taken to protect anonymity of subjects	**√Yes**	**No**
(b) Use of fetal tissue or abortus	**Yes**	**√No**			
(c) Use of organs or body fluids	**√Yes**	**No**			

PREPARATION OF AN ABSTRACT
FOR
NATIONAL RESEARCH ETHICS COMMITTEE (NREC)

This will be a double blind, placebo control, randomized control trial, conducted in Department of Hematology, DMCH for one year. Newly diagnosed ITP patients will be enrolled in the study after being selected by inclusion and exclusion criteria. Total sample size would be 100 (50 in each group). Enrolled patients would be divided into two groups (1:1) by block randomization. One group will get Eltrombopag& Prednisolone and other group will get Eltrombopag& Placebo. Researchers or any one related to the study in DMCH, patients & their attendants, no one will know which patient will get placebo or eltrombopag. Patient would be followed up on 1st, 2nd and 4th week of starting therapy. This clinical trial intends to find out role of eltrombopag as first line therapy when used with prednisolone in newly diagnosed patient. According to the requirement of Ethical Review Committee following topic has been answered.

1. *Describe the requirements in respect of the population and explain the rationale for using population of special groups such as children, Incompetent person or groups whose ability to give voluntary informed consent is questionable.*

Study population of this study are adult male & female (≥18 years), patient with newly diagnosed ITP attending OPD or IPD of department of hematology DMCH. Children shall be excluded from the study. There will be no inclusion of children, incompetent person or whose ability to give voluntary informed consent is questionable.

2. *Describe and assess any potential risks - physical, psychological, social, legal or other and assess the likelihood and seriousness of such risks. If methods of research create potential risks, describe other methods, if any, that were considered and why they cannot be used.*

Physical risk is minimum. Only physical risk is to any hazard during sample taking. There is no psychological risk. The study does not include any questions or procedure that can produce psychological trauma. There is no social harm. Diseases status and personal information of patients will be secret as per doctor-patient confidentiality. Costs of drugs and investigations will be provided from research fund. Patients will get compensation money (500 tk each) if there are any risks or loss of working time or privacy is involved in any particular procedure. So there will be no economic burden. There is no legal entanglement if they participate in the study.

3. *Describe procedures for protecting against or minimizing potential risks and assessment of their likely effectiveness.*

Newly diagnosed ITP patients with severe bleeding at presentation will not be included in the study as they need emergency rescue treatment. A Data and Safety Monitoring Board (DSMB) will be formed which will include two members of NREC, one biostatistician, one hematologist and one medicine specialist. Any adverse event (Drugs side effects- headache, weight gain, changes in liver enzymes, high blood sugar) or serious adverse event (grade 3 or grade 4 bleeding [26], hospitalization, thrombosis) will be delt with proper medical care.

4. *Include a description of the methods for safeguarding confidentiality or protecting anonymity.*

Every participant will be given an individual number. The participant will be known by that number throughout the study. In case record form participants will be identified by the number. Actual identity (name, address) of participants will be kept in a secret locker and only accessible by principal investigator. Anonymity of the participants will be maintained even after publication.

5. *When there are potential risks to the subject, or the privacy of the individual may be involved, the investigator is required to obtain a signed informed consent from the participant. For minors, informed consent must be obtained from the authorized legal guardian or parent of the subject. Describe consent procedures to be followed including how and where informed consent will be obtained.*

Informed written consent will be taken from patients. No minor person will be included in the study. So permission from legal guardian will not be necessary. Patient will be briefed extendedly by principal or co-investigator. Then they will be provided written consent form. After reading their questions will be answered and inquires will be addressed. If they agreed to participate in the study their sign will be taken in written form.

(a) *If signed consent will not be obtained, explain why this requirement should be waived and provide an alternative procedure such as a verbal consent.*

Signed consent will be obtained

(b) *If information is to be withheld from a subject, justify this course of action.*

No information will be withheld from subjects. Their chance of getting placebo will also be explained. They will be assure that they are getting treatment even in placebo group as 1st line drug prednisolone will be in both group.

(c) *If there is a potential risk to the subject or privacy of the individual or loss of work time is involved in any particular procedure, include a statement in the consent form stating whether any compensation will be available.*

There will be no potential risk except some side effects of drugs, which will be monitored. There will be an Institutional protocol safety board- A team of two doctors and one nurse will be assigned for supportive care of the study. Their contact number will be provided to the participants. So they can contact in any inquiry, confusion or emergency. Their anonymity will be maintained. We will not any extra time from them as they have to come in follow up even they were not in the study.

6. *If the study involves an interview, describe where and in what context the interview will take place. State approximate length of time required for the interview.*

Patient's history, examination and reports will be evaluated. It may take 10-15 minutes. We will do the interview and physical examination in OPD of department of hematology, DMCH.

7. *Assess the potential benefit to be gained by the individual subject as well as the benefits which may accrue to society in general as a result of the work. Indicate how the benefits may outweigh the risks.*

Patients can be benefited from free drugs (eltrombopag and prednisolone), free investigations (related to ITP), good supportive care and regular follow up. The study result may help to select suitable drug combination for future ITP patients. There are some risks like loss of time during follow up, weight gain, raised blood sugar. But it is more beneficial to treat ITP and reduce unnecessary risks of bleeding.

8. *In case of an experimental drugs, provide information about its status of registration for open sale in Bangladesh and in other developed countries.*

Prednisolone is a well-known drug and in use for a long time in Bangladesh. Eltrombopag is licensed to use in Bangladesh. Safety and efficacy of prednisolone and eltrombopag in ITP is

already established. Eltrombopag is approved in 80 counties for use in ITP.

9. *For experimental 'new' drugs* which are not registered in Bangladesh provide full information about the toxicity studies carried out in animals or human volunteers. Published papers on this regard shall be annexed.*

Prednisolone and eltrombopag both are registered in Bangladesh for use.

10. *If placebo is to be used justify its uses and why the study cannot be done without its use.*

Placebo is used to avoid dissatisfaction of the patients. If placebo is it used, one group will get prednisolone only and patient of that group can think one drug may not be enough for treatment. If we give placebo and patients, researchers both are blinded they have nothing to worry about.

11. *If an experimental 'new' drug is to be used give a statement regarding its sponsorship and the conditions for such sponsorship.*

Prednisolone and eltrombopag both are registered in Bangladesh for use. However, both drug for the study will be provided by Renata limited Bangladesh. There are no terms with the pharmaceutical in exchange of drugs and financial support. MOU with Renata limited is attached in appendix.

12. *State if the activity requires the use of records (hospital, medical, birth, death or other), organs, tissues, body fluids, the fetus or the abortus.*

There will be no use of hospital, medical, birth, death or other records. No organs, tissues, the fetus or the abortus will be used in the study. Only blood will be taken for investigations.

RESEARCH PROPOSAL

Title: Efficacy of Eltrombopag & Prednisolone Versus Prednisolone Monotherapy in Newly Diagnosed Immune Thrombocytopenia- A Randomized Control Trial.

Summary: This will be a double blind, placebo control, randomized control trial, and conducted in Department of Hematology, DMCH for one year. Newly diagnosed ITP patients will be selected after meeting inclusion and exclusion criteria, they will be thoroughly informed about the study, used drugs, randomization, risk and benefits, follow up. If they agree to participate in the study, their consent will be taken and they will be enrolled in the study. Detail history and clinical exam will be done. Key points are- History of spontaneous bleeding in last month, History of vaccination, History of recent viral infection, fever, Presence of organomegaly. Primary investigation will be- CBC PBF, RBS, ANA, TSH, Anti *H. pylori*IgG, Anti-HCV, APTT, BMS (if indicated). Main outcome variable will be platelet count and number of spontaneous bleeding. Total sample size would be 100 (50 in each group). Enrolled patients would be divided into two groups (1:1) by block randomization. One group will get Eltrombopag& Prednisolone and other group will get Eltrombopag& Placebo. Researchers or any one related to the study in DMCH, patients & their attendants, no one will know which patient will get placebo or eltrombopag. Only respectable third party will know the information. Patient would be followed up on 1st, 2nd and 4th week of starting therapy. Patient would be evaluated in every follow up by history, physical examination and investigation. History of any spontaneous bleeding event, any discomfort or new symptoms science last follow up will be noted. General examination will be performed in every follow up. CBC and RBS will be done in every follow up. Institutional protocol safety board will be responsible for monitoring and management of any adverse event. Data will be collected on predesigned case record form and

will be collected by face-to-face interview, physical examination and collecting laboratory reports. After data collection data will be edited, cleaned and prepared for analysis at the end of the study. The statistical analysis will be conducted using SPSS (statistical package for the social science) version 25 statistical software. The result of the study may help to increase treatment response rate in newly diagnosed ITP. This could increase durability of first line treatment and decrease relapse. The result of the study will be published in national and international journals.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets and suppression of platelet production. The diagnosis of ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy. A platelet count (Plt) less than 30 x 10^9/L generally indicates severe disease. ITP is said to be ‘‘newly diagnosed’’ if time of presentation from the diagnosis is within 3 months, “persistent” if within 3-12 months and chronic if lasting for more than 12 months.

The mechanisms behind ITP are complex and poorly understood, although it is well known that antiplatelet autoantibodies play a central role. An altered response by splenic T follicular helper cells induce proliferation and differentiation of auto reactive B-cells.These produce antiplatelet autoantibodies, predominantly of the immunoglobulin (Ig)G isotype, which are able to react with a series of platelet receptors, mainly glycoprotein (GP) Iib/IIIa and GPIb/IX, but also GPV, GPIa/Iia, or GPIV. These antigen-antibody complex induce cell destruction. The course of the disease may vary in each individual case according to the specific autoantibodies, and targeted

surface glycoproteins, which determine the nature of the prevailing pathogenic mechanism (i.e. accelerated clearance, inhibited megakaryopoiesis or platelet apoptosis). The covered platelets experience splenic sequestration and subsequent phagocytosis by mononuclear macrophages. Macrophages still play an additional harmful role in ITP since they behave as the main antigen-presenting cell. On the other hand, CD8+ T-cells also contribute to thrombocytopenia by increasing platelet apoptosis. Recently, the Ashwell–Morell receptor (AMR), which is an asialoglycoprotein counter receptor predominantly expressed in hepatocytes, has also been shown to play an important role in anti-GPIbα-antibody-mediated platelet clearance. As a consequence, the circulating half-life of platelets is markedly reduced. Furthermore, bone marrow megakaryocytes are unable to produce platelets normally, which exacerbates thrombocytopenia: on the one hand, there is an autoimmune response against megakaryocytes;[3] on the other hand, the circulating thrombopoietin (TPO), which is the main growth factor of megakaryocytes, does not increase to a level high enough to stimulate the production of these at the required rate.

First-line treatment options for ITP usually include corticosteroids (dexamethasone, prednisone) and immunoglobulins [intravenous immunoglobulin (IVIG), Rho(D) immune globulin (anti-D)], which produce fast but transient responses. Corticosteroids show an initial response in 60–70% of patients within 2–14 days, but the response often lasts <6 months.[11] IVIG will produce a response in 1–3 days in 90% of patients, but the response typically lasts only 2–4 weeks.

For patient's refractory to first-line treatments, common therapeutic options include TPO-Ras (thrombopoietin receptor agonist), the anti-CD20 antibody rituximab, splenectomy, and immunosuppressive agents (azathioprine, cyclosporine A (CSA), cyclophosphamide, danazol, dapsone, mycophenolatemofetil, and vincristine).

TPO-Ras are the only therapeutic option for ITP that increases platelet production. In addition to promoting platelet production from existing megakaryocytes, TPO-Ras may also enhance proliferation of megakaryocytes in bone marrow, as suggested by in vitro studies and clinical trials in patients with aplastic anemia. Importantly, TPO-Ras may reduce platelet destruction by restoring Treg (regulatory T cell) and regulatory B-cell activity, thereby attenuating the autoimmune response to platelets. In patients treated with TPO-Ras for >3 months, Treg activity was significantly improved compared with the pretreatment group ($p = 0.001$) and was similar to the Treg activity in healthy subjects ($p = 0.9$).[14] Moreover, preliminary evidence suggests that autoantibody levels in patients with ITP may progressively decrease with TPO-RA treatment, which may contribute to restoration of immune tolerance to platelets.

Eltrombopag is an oral Thrombopoietin Receptor Agonist (TPO-RA) which is approved for use in more than 80 countries, including the United States and European Union countries. In randomized, controlled trials, eltrombopag has been shown to safely and durably increase platelet count in both adults and children with refractory ITP. Clinical evidence from patients who received eltrombopag for up to 8.8 years supports that eltrombopag retains its safety and efficacy with long-term continuous use, even though it would be necessary to evaluate further related events associated with eltrombopag for a longer term.

Improving the efficacy and durability of first-line treatments would reduce the number of patients who fail therapy and, therefore, help spare them from the burdensome ‘trial and error’ period. Several clinical trials studied role of eltrombopag as first line treatment in combination with other agents eg- dexamethasone, rituximab. Gómez- Almaguer et al. studied role of eltrombopag and high-dose dexamethasone as frontline treatment of newly diagnosed ITP in adults. [1] Another studied role of eltrombopag, low dose rituximab, and dexamethasone

combination as frontline treatment of newly diagnosed ITP. [2] Margo et al studied role of eltrombopag and High-dose dexamethasone in chronic ITP. [3]

This study intends to find out role of eltrombopag as first line therapy. In this study we shall compare response of prednisolone and eltrombopag against prednisolone as first line treatment in newly diagnosed ITP.

Research objectives

General objective

To determine efficacy of eltrombopag & prednisolone over prednisolone monotherapy in newly diagnosed patients with immune thrombocytopenia by accessing change in platelet count and number of spontaneous bleedings.

Specific objectives

- To determine response of eltrombopag and prednisolone in increasing platelet count and reducing incidence of spontaneous bleeding in newly diagnose ITP patients.
- To determine response of prednisolone alone in increasing platelet count and reducing incidence of spontaneous bleeding in newly diagnose ITP patients.
- To compare response of eltrombopag &prednisolone group and prednisone alone group.

Hypothesis

Eltrombopag and prednisolone combination is more efficacious than prednisolone alone as a first line treatment in newly diagnosed patients with ITP.

Rationale of the study

ITP is not uncommon in our country. Prednisolone is the most used drug in first line therapy and it shows initial response of 70-80%. [4] We want to improve the response rate of first-line treatment by adding eltrombopag with prednisolone. Though eltrombopag is recommended for second line therapy, some studies use eltrombopag as first line therapy. A single-arm study of dexamethasone in combination with 4 weeks of eltrombopag used upfront in adult patients with newly diagnosed ITP produced 90-100% response at completion of therapy and 66.7% relapse-free survival at 1 year. [1] A phase 3 randomized trial of eltrombopag versus standard first line pharmacological management for newly diagnosed ITP in children is currently going on. [5] Our main objective is to find out the efficacy of eltrombopag and prednisolone against prednisolone alone as first line treatment in newly diagnosed ITP

Methodology

Study design: A double blind, placebo control, Randomized Clinical Trial

Study period: One year

Place of study: Department of Hematology and Bone Marrow Transplant Unit, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh.

Study population: Newly diagnosed ITP patients attending OPD and IPD of Department of Hematology and Bone Marrow Transplant Unit, Dhaka Medical College and Hospital (DMCH), Dhaka.

Selection criteria

Inclusion criteria:

1. Patients with newly diagnosed ITP
2. Platelet Count $\leq 30x10^9/L$
3. Age between 18 to 70 years.

Exclusion criteria:

1. Persistent or chronic ITP
2. Pregnant women
3. Secondary ITP- ITP due to SLE, Anti-phospholipid syndrome, Evans syndrome, HCV or *H Pylori* associated ITP.
4. History of vaccination, recent viral infection, fever
5. Evan's Syndrome
6. Known case of chronic renal failure or liver diseases
7. Grade 3 or 4 bleeding at presentation.

Sampling technique: Block Randomization

Sample Size

The sample size was determined by using the following formula

$$n = \frac{P1(100 - P1) + P2(100 - P2)}{(P1 - P2)^2} \times (Z_{\propto} + Z_{\beta})^2$$

P1= Experimental Group (Eltrombopag and Prednisolone) Response – There is no such study found but Eltrombopag and dexamethasone in first line therapy showed 90-100% response. [1] We want to consider P1 as 90% for sample size calculation.

P2= Control Group (Prednisolone only) Response- Prednisolone as first line therapy shows 70-80% response. [4] We want to consider P2 as 70% for sample size calculation.

$Z_{\propto}$ = level of significance. For this study we want 5% level of significance. The value would be 1.96

Z_{β} = given power. For this study we want 80% power. The value would be 0.842

$$n = \frac{90 \times 10 + 70 \times 30}{(95 - 75)^2} \times (1.64 + 0.84)^2$$

$$n = \frac{3000}{400} \times 6.15$$

$$n = 46.12$$

46 participants in each group. We want to consider attrition 10%. So, sample of one group will be 46+4 = 50 and total sample would be 50+50=100.

Variables

1. Independent Variable
    - Age
    - Sex
    - Occupation
    - Home District
2. Dependent Variables-

Main Outcome variables

- Changes in Platelet count
- Spontaneous bleedings

Other associated variables

- Changes in hemoglobin
- Changes in Total WBC count

3. Confounding variables
    - DM
    - Ischemic heart diseases
    - Thyroid diseases
    - any other auto-immune diseases e.g. vitiligo.

Study procedure

After meeting inclusion and exclusion criteria patients will be thoroughly informed about the study, used drugs, randomization, risk and benefits, follow up. If they agree to participate in the study, their consent for this study will be taken and they will be enrolled in the study.

Detail history and clinical exam will be done. Key points are- History of spontaneous bleeding in last month, History of vaccination, History of recent viral infection, fever, Presence of organomegaly.

Primary investigation will be- CBC PBF, RBS, ANA, TSH, Anti *H. pylori*IgG, Anti-HCV, APTT, BMS (if indicated)

NB:

1. If APTT is more than 10 sec of control, patient would be evaluated for Anti-Phospholipid Syndrome by anti-cardiolipin Antibody and Anti-beta$_2$ glycoprotein1 Antibody
2. If Hemoglobin in less than 11.5gm/dL patient would be evaluated for Anemia by Iron Profile or Coomb's Test based on CBC parameter and PBF findings]

Randomization: Enrolled patients would be divided into two groups (1:1) by block randomization. Block Randomization would be done by computer generated pattern. One such plan has attached in appendix III, page 49 as a sample. Actual randomization plan will be provided by Renata limited team who know about eltrombopag and placebo. Randomization allocation delivered only to the enrolling site study staff. A voluntary nurse will be in charge of enrolling the patients according to randomization plan.

Blinding and placebo control: It will be a double-blind study. Researchers nor participants will know who is getting placebo/eltromopag. One group will get Prednisolone & Eltrombopag and another group will get Prednisolone & Placebo. Eltrombopag, Prednisolone and Placebo will be provided by Renata Limited Bangladesh and patient will get at free of costs. Placebo will have same size, shape, color, markings, taste, smell and packaging like Eltrombopag. Eltrombopag and placebo will be provided in separate color-coded box marked-A (red) or B (green). Group A and Group B participants will be given colored cards (red and green) for identification. They will receive tablets from marked box. Researchers or any one related to the study in DMCH, patients & their attendants no will know which box contain placebo or eltrombopag. Only respectable person of Renata limited will know the information. The team who knows the information will be head by their CEO. At the end point all data will be submitted to the team who know about placebo.

Experimental Group - Eltrombopag& Prednisolone Control Group - Prednisolone and Placebo

Dose- Prednisolone 1mg/kg/day for 28 days Eltrombopag/Placebo 25mg/day for 28 days

Follow Up-

Follow up at the end of 1st week, 2nd week and 4th week

Patient would be evaluated in every follow up by history, physical examination and investigation. History of any spontaneous bleeding event, any discomfort or new symptoms science last follow up. General examination will be performed in every follow up. CBC, RBS, ALT, AST and creatinine will be done in every follow up.

Primary End Point-28 days after starting therapy. Complete Response is expected after 28 days of therapy.

Patient would continue therapy and follow up in OPD but would not be included in the study.

Supportive care and rescue-

A Data and Safety Monitoring Board (DSMB) will be formed which will include two members of NREC, one biostatistician, one hematologist and one medicine specialist. Any adverse event (Drugs side effects- headache, weight gain, changes in liver enzymes, high blood sugar) or serious adverse event (grade 3 or grade 4 bleeding, hospitalization, thrombosis) will be delt with proper medical care.

If any patient shows no response within 14 days and has grade 3 or 4 bleeding, rescue with methyl prednisolone or IV Ig would be given and discontinued from study. If group A patient reaches platelet count >400x10^9\L, eltrombopag will be stopped.

Pharmacodynamics and pharmacokinetics of Eltrombopag and Prednisolone

Pharmacodynamics and pharmacokinetics of Eltrombopag and Prednisolone is attached in appendix

Data Collection-

Data will be collected on predesigned case record form and will be collected by face-to-face interview, physical examination and collecting laboratory reports.

Operational Definition-

ITP- Widely accepted abbreviation, ITP, has variably been defined as "immune thrombocytopenic Purpura," "idiopathic thrombocytopenic Purpura," and, most recently, "immune thrombocytopenia." It is an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets most commonly occurring in response to an unknown stimulus. ITP may occur in isolation (**primary**) or in association with other disorders (**secondary**). Secondary causes include- Systemic lupus erythematosus, Antiphospholipid syndrome, Autoimmune thrombocytopenia (eg, Evans syndrome), Infection with cytomegalovirus, *H. pylori*, hepatitis C, HIV, varicella zoster, Lymphoproliferative disorders, Vaccination side effect.

Newly diagnosed, Persistent and Chronic ITP-Newly diagnosed ITP is considered as lasting up to 3 months, followed by persistent (3-12 months) and chronic disease (12 months).

Complete response (CR) – A platelet count $\geq 100x10^9$/L and the absence of bleeding.

Partial Response–A platelet count $\geq 30x10^9$/L and a greater than 2-fold increase in platelet count from baseline and the absence of bleeding.

No response (NR) –A platelet count <$30x10^9$/L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding.

Indication of BMS in ITP- No response or relapse following first-line therapy, presence of atypical clinical or laboratory features, Age >60 years, before splenectomy

Grade 3 bleeding- Bleeding requiring blood transfusion &\or associated with moderate hemodynamic instability.

Grade 4 bleeding- Bleeding with severe hemodynamic instability, internal organ bleeding, CNS bleeding.

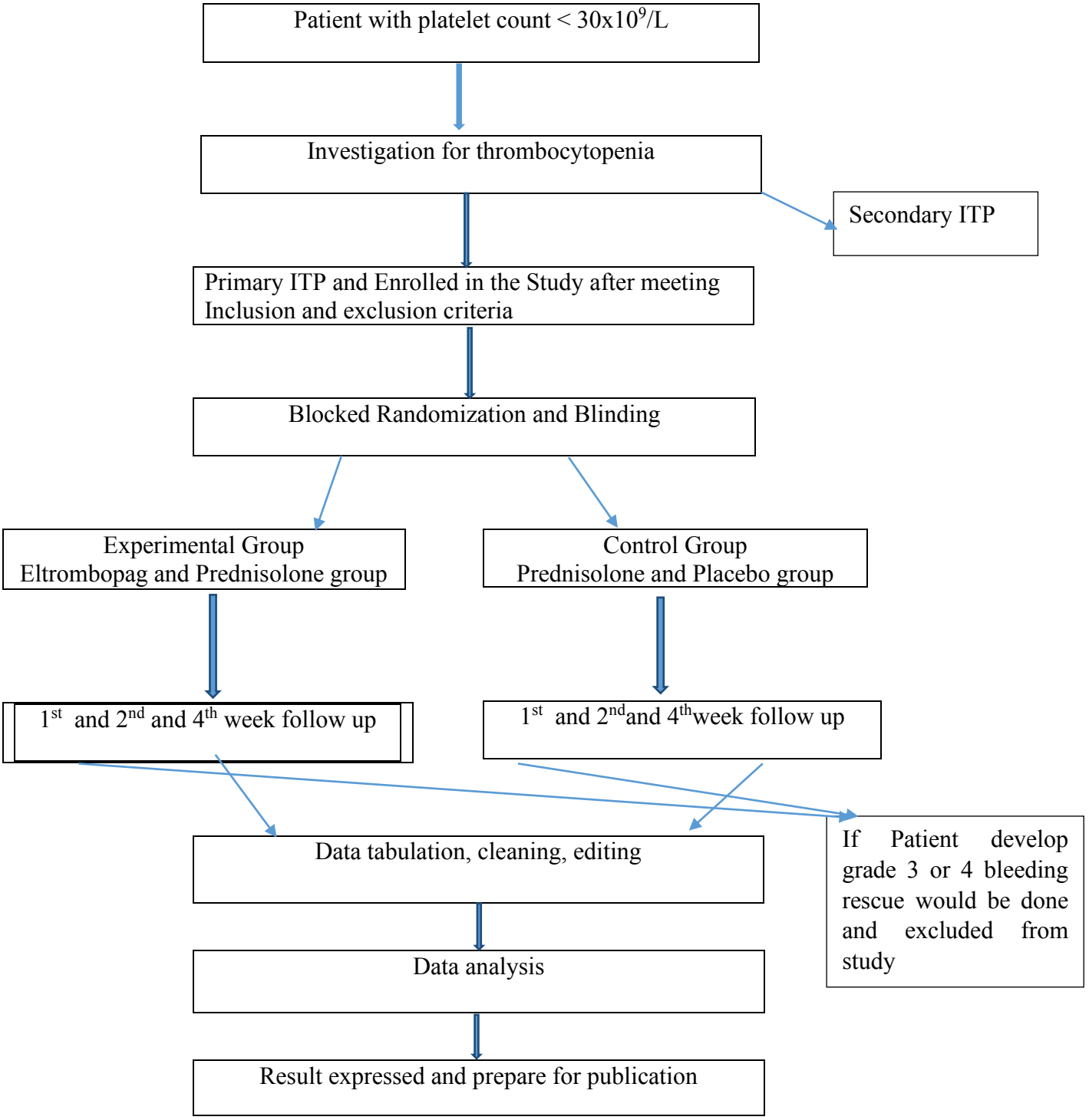
Utilization of Results: The result of the study may help to increase treatment response rate in newly diagnosed ITP. It can help to establish Eltrombopag as first line therapy. This could increase durability of first line treatment and decrease relapse. The result of the study will be published in national and international journals.

Facility: The study will be conducted in department of hematology and BMT unit, DMCH. Study population are newly diagnosed ITP patients attending our OPD and IPD. Their sample for investigation will be collected by technologist of our department. CBC will be done in our department with Sysmex XN-2000 auto analyzer. Team of volunteer doctor and nurse will be responsible for managing any clinical emergency of the patients. The drugs and placebo will be stored in our department. Some investigation facility is not available in our department. These investigations will be carried out in BSSMU.

Statistical Analysis Plan

After data collection data will be edited, cleaned and prepared for analysis at the end of the study. At the end of the study, all data will be submitted to the team who know about placebo/eltrombopag. The statistical analysis will be conducted using SPSS (statistical package for the social science) version 25 statistical software. The findings of the study will be presented by frequency and percentage in tables. Means and standard deviations for continuous variables and proportion for categorical variables will be used to describe the characteristics of the total sample. Association between two qualitative variables will be assessed by Chi-square test, where $p<0.05$ with 95% confidence level will be considered as significant. Appropriate statistical tests will be done to interpret the findings of the study.

Flowchart


Patient with platelet count < 30x10^9/L
Investigation for thrombocytopenia
Secondary ITP
Primary ITP and Enrolled in the Study after meeting Inclusion and exclusion criteria
Blocked Randomization and Blinding
Experimental Group Eltrombopag and Prednisolone group
Control Group Prednisolone and Placebo group
1st and 2nd and 4th week follow up
1st and 2nd and 4th week follow up
If Patient develop grade 3 or 4 bleeding rescue would be done and excluded from study
Data tabulation, cleaning, editing
Data analysis
Result expressed and prepare for publication

Work schedule

Activity ↓ (months →)	1st	2nd	3rd	4th	5th	6th	7th	8th	9tth	10th	11th	12th
Literature review												
Study design and protocol writing												
IRB/BMRC clearance												
Patient selection and enrollment												
Collection of data												
Data cleaning, editing,												
Data analysis												
Preparing result and writing for publication												

Ethical consideration

- Before starting this study, the research protocol will be submitted and approved by the Institutional Review Board of DMCH, Dhaka and national research ethics committee, BMRC.
- Eltrombopag is an oral TPO-RA approved for use in more than 80 countries, including the United States and European Union countries.[16] Prednisolone is widely used drug. We are not exposing patient to any new drugs which safety and efficacy is not well established.
- All participants will be informed about the objectives, methodology and purpose of the study in an easily understandable way.
- All information regarding benefits and hazards regarding the study will be delivered to the all participants & only those who agree to participate will be included in the study.
- Verbal and written consents will be obtained from all participants without any influences prior to data collection.
- Data obtained from the study will be used only for research purposes. The confidentiality of all study information will be maintained strictly.
- Participants can withdraw themselves from the study at any time even after giving consent.

Reference

1. Gómez-Almaguer D, Herrera-Rojas MA, Jaime- Pérez JC, et al. Eltrombopag and high-dose dexamethasone as frontline treatment of newly diagnosed immune thrombocytopenia in adults. Blood 2014; 123: 3906–3908.
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3. Magro D, Levato L, Eugenio P, et al. Highdose dexamethasone and eltrombopag in chronic immune thrombocytopenia: a single institution experience. Haematologica 2017; 102: 1–217.
4. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168–86.
5. Kristin A. Shimano, Rachael F. Grace, Carolyn M. Bennett, Robert J Klaassen, Cindy Neunert, et al; A Phase 3 Study of Eltrombopag Vs. Standard First-Line Management for Newly Diagnosed Immune Thrombocytopenia in Children. Blood 2019; 134 (Supplement_1): 2369. Doi: https://doi.org/10.1182/blood-2019-125487

INFORMED CONSENT FORM

This consent form informed the participants about the necessary information, pro and con of the research and help the participants to make decision.

Name of the study: "Efficacy of Eltrombopag & Prednisolone versus Prednisolone Monotherapy in Newly Diagnosed Immune Thrombocytopenia- A Randomized Control Trial**."**

Chief Researcher: Dr. Md. Manirul Islam, Associate Professor, Hematology Department & BMT Unit, DMCH.

Associate Researcher: Dr Gazi Yeasinul Islam, Medical Officer, Hematology Department & BMT Unit, DMCH.

Purpose of the study: To determine efficacy of eltrombopag & prednisolone over prednisolone monotherapy in newly diagnosed patients with immune thrombocytopenia.

Data Provider: Patient himself/herself.

Role of Participants: At first Patient will be evaluated for the eligibility criteria with some questions & some investigations. Participants will be divided into two groups. Patient or researcher cannot choose groups. It will be done randomly. One group will get prednisolone & eltrombopag and other group will get prednisolone and placebo (it has no pharmacological effect). Neither researcher nor participants will know which group will get placebo. Even if

you get placebo, only prednisolone is enough for your treatment, you will not be untreated.Patient has to take the drugs orally. He/She has to come for follow up at 1th, 2th& 4th week after starting drug. In every follow up he/she will be evaluated by physical examination & investigation. Patient has to follow some rules when he/she is taking drug. Violation of some rules will disqualify him/her for the study. All investigations and drugs will be provided from researchers.

Eltrombopag and Prednisolone as a drug: These drugs is to take orally daily. These drugs has used in different trials all over the world. Both drug has approval to use in different countries including ours.

Benefit of the participant in the research: only prednisolone as first line therapy has success rate of 70-80%. We want to add eltrombopag to achieve success rate of 90-100%

Risks & discomforts: Risks of participating in this study is almost zero. Eltrombopag is safe in humans, is proven by many studies. Even after that we will investigate any adverse effect in every follow up. Nothing will be done that can is harmful for your health. There will be a team of doctors and nurse to monitor their health, any adverse reaction and answering any inquiries. Team members contact number will be provided to you.

Alternate Treatment: If you are not interested in the study, alternate treatment options will be offered. You will never be treated differently.

Incentives & cost of drugs: All investigations and drugs will be provided from researchers during the research period.

Confidentiality: Your personal, disease, treatment & outcome related all information will be confidential during & after the study. Information related to research will be published anonymously.

Voluntary Participation: Participation in this research is fully voluntary. You can with draw yourself at any stage of research. Your rights of treatment will always be preserved.

Related question: Please let us know if you have any question. If you feel like throwing any question in future, then please contact researcher.

Dr Mohammad Manirul Islam
MBBS, FCPS (Hematology)
Associate Professor
Department of Hematology & BMT Unit,
Dhaka Medical College and Hospital, Dhaka

Informed consent

I, the below signing person, read / listen to the information of consent form. I have understood the process of the study in sound mind. I have clarified other queries by asking questions. I am willing to participate in this study voluntarily, in sound mind.

I clearly understand that participation is voluntary, harmless, helpful for me & other patients in the future.

Participant Sign or Thumb impression	Witness sign or Thumb impression	Signature of Researcher

Case Record Form

Efficacy of Eltrombopag & Prednisolone versus Prednisolone Monotherapy in Newly Diagnosed Immune Thrombocytopenia- A Randomized Control Trial.

Data Number- Randomization number-

[Please mark with a marker]

☐ **Group-A**

☐ **Group- B**

Co- Morbidity- IHD, HTN, DM, Thyroid diseases, any other autoimmune diseases-

	No	Yes	Specify
History of spontaneous bleeding in last month			How many episode- Bleeding sites-
History of vaccination			
History of recent viral infection, fever (within one month)			Mention if infectious agent is known
Presence of Organomegaly- (Liver, spleen or other)			

Primary Investigations-

CBC- Hb- MCV- TC- ANC- -		
PBF		
RBS-	ANA-	TSH-
Anti *H. pylori*IgG-	Anti-HCV-	APTT-
BMS-		

	Primary	1st follow up	2nd follow up	3rd follow up
Platelet Count				
MPV				
PWD				
Weight				
RBS				
TC ANC				
Hemoglobin				
ALT AST				
S. Creatinine				
Spontaneous Bleeding				

Note:

Data Collected By-

Name-

Designation-

Address-

Procedure of maintaining confidentiality

- Patient's name, address, phone number other information will be kept in different master record book.
- Patients shall be provided a small card containing their code number, group, follow up date, emergency contact number.
- Case record form will contain a code number. During data collection and analysis patients will be recognized by that number only.
- Access to master record book would be limited
- Maser record book will be stored in a separate cabinet.
- Electronic data are stored in password-protected computers or files
- No identity of participants will be exposed to any outside person.
- Diseases and treatment history of the patient will be confidential.
- Data will be stored as per advice of data monitoring and safety board.
- Proper consent will be taken in the presence of a witness in a closed room.
- Privacy of the patient will be maintained.

A Sample of Randomization Plan From

1. Group B
2. Group A
3. Group B
4. Group A
5. Group B
6. Group B
7. Group A
8. Group A
9. Group B
10. Group A
11. Group B
12. Group A
13. Group A
14. Group B
15. Group A
16. Group B
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20. Group A
21. Group A
22. Group B
23. Group B
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43. Group B
44. Group A
45. Group A
46. Group B
47. Group A
48. Group B
49. Group A
50. Group B
51. Group B
52. Group B
53. Group A

54. Group A_____
55. Group A_____
56. Group B_____
57. Group A_____
58. Group A_____
59. Group B_____
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85. Group B_____
86. Group A_____
87. Group A_____
88. Group B_____
89. Group A_____
90. Group B_____
91. Group A_____
92. Group B_____
93. Group B_____
94. Group A_____
95. Group B_____
96. Group A_____
97. Group A_____
98. Group B_____
99. Group A_____
100. Group B_____

100 subjects randomized into blocks of102242281042 28448 2 284 10
2

Appendix

Pharmacokinetics and Pharmacodynamics of Eltrombopag and Prednisolone

Eltrombopag

Eltrombopag is a thrombopoietin receptor agonist used to treat thrombocytopenia or aplastic anemia associated with various etiologies.

Mechanism of Action- Eltrombopag is an orally bioavailable, small-molecule TPO-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor. Eltrombopag is a stimulator of STAT and JAK phosphorylation. Unlike recombinant TPO or romiplostim, Eltrombopag does not activate the AKT pathway in any way. It should be noted that when given to patients with aplastic anemia, other lineages besides platelet count were increased, suggesting that either eltrombopag enhanced the effect of TPO in vivo; or there is a yet uncovered mechanism of action at work

Absorption- Peak absorption of Eltrombopag occurs around 2-6 hours following oral administration, and the total oral absorption of drug-related material following a 75 mg dose was estimated to be at least 52%.

Volume of distribution- Based on a radiolabel study, the concentration of eltrombopag in blood cells is approximately 50% to 79% of plasma concentrations. Eltrombopag is highly protein bound (>99%).

Metabolism- Eltrombopag is predominantly through pathways including cleavage, oxidation, and conjugation with glucuronic acid, glutathione, or cysteine. In vitro studies suggest that CYP1A2

and CYP2C8 are responsible for the oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag

Elimination-Eltrombopag is eliminated primarily via the feces (59%), along with 31% being renally excreted.

Side effects

Hepatotoxicity – may increase liver enzymes

Thromboembolic complication- portal vein thrombosis has been reported in some cases of CLD.

Most common adverse side effects are nausea, diarrhoea, upper respiratory tract infection, vomiting, myalgia, UTI, anaemia, fatigue, headache.

Pharmacokinetics and Pharmacodynamics of Prednisolone

Prednisolone is a glucocorticoid used to treat adrenocortical insufficiency, inflammatory conditions, and some cancers.

Pharmacodynamics- Corticosteroids bind to the glucocorticoid receptor, inhibiting pro-inflammatory signals, and promoting anti-inflammatory signals. Prednisolone has a short duration of action as the half life is 2.1-3.5 hours. Corticosteroids have a wide therapeutic window as patients make require doses that are multiples of what the body naturally produces. Patients taking corticosteroids should be counselled regarding the risk of hypothalamic-pituitary-adrenal axis suppression and increased susceptibility to infections.

Mechanism of action- The short term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of

inflammation. Corticosteroids binding to the glucocorticoid receptor mediates changes in gene expression that lead to multiple downstream effects over hours to days.

Glucocorticoids inhibit neutrophil apoptosis and demargination; they inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit NF-Kappa B and other inflammatory transcription factors; they promote anti-inflammatory genes like interleukin-10.

Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. High doses of glucocorticoids for an extended period bind to the mineralocorticoid receptor, raising sodium levels and decreasing potassium levels.

Absorption - Oral prednisolone reaches a C_{max} of 113-1343ng/mL with a T_{max} of 1.0-2.6 hours.[1] Oral prednisolone is approximately 70% bioavailable.

Volume of distribution- A 0.15mg/kg dose of prednisolone has a volume of distribution of 29.3L, while a 0.30mg/kg dose has a volume of distribution of 44.2L

Protein Bound- Prednisolone's protein binding is highly variable, ranging from 65-91% in healthy patients.

Mechanism- Prednisolone can be reversibly metabolized to prednisone which is then metabolized to 17α,21-dihydroxy-pregnan-1,4,6-trien-3,11,30-trione (M-XVII), 20α-dihydro-prednisone (M-V), 6βhydroxy-prednisone (M-XII), 6α-hydroxy-prednisone (M-XIII), or 20β-dihydro-prednisone (M-IV). 20β-dihydro-prednisone is metabolized to 17α,20ξ,21-trihydroxy-5ξ-pregn-1-en-3,11-dione(M-XVIII). Prednisolone is metabolized to Δ6-prednisolone (M-XI), 20α-

dihydro-prednisolone (M-III), 20β-dihydro-prednisolone (M-II), 6αhydroxy-prednisolone (M-VII), or 6βhydroxy-prednisolone(M-VI). 6αhydroxy-prednisolone is metabolized to 6α,11β,17α,20β,21-pentahydroxypregnan-1,4-diene-3-one (M-X). 6βhydroxy-prednisolone is metabolized to 6β,11β,17α,20β,21-pentahydroxypregnan-1,4-diene-3-one (M-VIII), 6β,11β,17α,20α,21-pentahydroxypregnan-1,4-diene-3-one (M-IX), and 6β,11β,17α,21-tetrahydroxy-5ξ-pregn-1-en-3,20-dione (M-XIV). MVIII is metabolized to 6β,11β,17α,20β,21-pentahydroxy-5ξ-pregn-1-en-3-one (M-XV) and then to MXIV, while MIX is metabolized to 6β,11β,17α,20α,21-pentahydroxy-5ξ-pregn-1-en-3-one (M-XVI) and then to MXIV. These metabolites and their glucuronide conjugates are excreted predominantly in the urine

Route of excretion: Prednisolone is over 98% eliminated in urine

Plasma half Life: Prednisolone has a plasma half life of 2.1-3.5 hours. This half life is shorter in children and longer in those with liver disease