Cover Page

Official Title of the study

The Safety and Efficacy of Mini-Pool IVIG as Loading and Maintenance Therapy for Children with Persistent Immune Thrombocytopenia: A Novel Approach for Low-Middle Income Countries

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The Safety and Efficacy of Mini-Pool IVIG as Loading and Maintenance Therapy for Children with **Persistent** Immune Thrombocytopenia, A Novel Approach for Low-Middle income countries

Introduction:

Immune thrombocytopenia (ITP) occurs with an incidence rate of 1.6 to 3.9 per 100,000 patient-years, which increases with age and has a slight female preponderance [1]
It is an autoimmune disease characterized by an isolated decrease in the platelet count and an increased risk of bleeding. The pathogenesis is complex, affecting multiple components of the immune system and causing both peripheral destruction of platelets and impaired megakaryopoiesis in bone marrow. The diagnosis is typically made by excluding known thrombocytopenia causes. ITP can affect both children and adults. The American Society of Hematology (ASH) defines ITP as a generalized purpuric rash accompanied by a platelet count less than 100,000/µL and normal white blood cell (WBC) count and hemoglobin level. Primary ITP may be further categorized based on the timing and persistence of symptoms. Newly diagnosed ITP refers to the condition from the time of diagnosis to 3 months afterward. Persistent ITP arises when symptoms continue 3 to 12 months following the initial diagnosis. Chronic ITP indicates ongoing symptoms beyond 12 months from the initial diagnosis until resolution or further management. Refractory ITP includes cases that do not resolve with splenectomy, Severe thrombocytopenia, when platelet counts are below 20,000/µL, warrants medical treatment [2].

Management strategies have evolved significantly, emphasizing individualized treatment approaches based on disease severity, bleeding risk, and patient-specific factors. The latest therapeutic options, ranging from observation and first-line treatments such as corticosteroids and intravenous immunoglobulin (IVIG) to second-line therapies, including thrombopoietin receptor agonists and immunosuppressive agents.

The balancing of treatment efficacy with the potential side effects and long-term outcomes is very crucial for optimum management. There is emerging role of personalized medicine in optimizing care for children with ITP, highlighting recent advances in targeted therapies and the potential for future research to refine diagnostic and treatment paradigms [3].
Eltrombopag (ELT) is effective and safe in adult persistent/chronic immune thrombocytopenia (p/cITP); a proportion could achieve a sustained response off treatment (SRoT). A multicentre retrospective observational study was performed in November 2022 for children with p/cITP who used ELT alone for >2 months between January 2017 and November 2021. Clinical data of pre-, during and post-ELT were collected. SRoT was defined as maintaining a platelet count of ≥30 × 10(9) /L without rescue therapy for at least 6 months off ELT. There were 43.3% and 25.9% achieved complete response (CR) and response (R). [4].

While IVIG is considered as safe and effective first line therapy for management of acute pediatric/adult ITP [5], yet there is no report on the role of IVIG as second line therapy for persistent/chronic ITP. One of the reasons might be the high cost of IVIG therapy compared to other standard therapies. El Ekiaby et al published a method for preparation of IVIG from mini-pools of plasma in blood bank environment using disposable medical devices produced by Swiss Company VIPS. The devices combine single use disposable bags and validated virus inactivation and IgG purification chemicals [6]. Mini-pool immunoglobulins proved safety and efficacy for management of acute pediatric ITP in a prospective randomized clinical trial [7]. The use of this new technology significantly reduces the cost of production of local mini-pool IVIG preparations. The use of locally produced mini-pool IVIG might be a safe and cost effective second line therapy.

Aim of the study:
Assessment of safety and efficacy of mini-pool IVIG as a second line therapy for management of pediatric persistent ITP.

Primary end points:
1-Bleeding score, duration, site and frequency calculated as BAT score
2-Frequency of hospital admission due to ITP critical bleeding episodes excluding hospital admission for Mini-Pool IVIG administration
3-Levels of platelet count during study period and its maintenance during subsequent 6 months after end of study period for patients with PC >30,000/uL

Secondary end points:
1-Record of adverse events
2-Patient/family satisfaction
3-School attendance and physical activity
4- Presence of a sustained response

Study protocol:
Three tertiary care Pediatric Hematology/Oncology centers will be enrolling children with persistent ITP “loss of initial response to first line therapy (steroids/IVIG) within 3-6 months”

Participating centers are, Ain Shams, Zagazig and Assuit Pediatric Hematology/Oncology

Inclusion Criteria:
-Age 1 – 10 years
-Gender: Males and Females
-Persistent ITP according to ASH definition
-No history of treatment with thrombopoietin agonists

Exclusion criteria:
-History of severe drug adverse events to IVIG
-Previous history of ICH
-Difficult venous access
-Congenital thrombocytopenia, secondary ITP and non-immune thrombocytopenia

Sample size
20 child with persistent ITP

6-Study period 3 – 6 months followed by 6 months observation for cases that showed remission off-therapy (SRoT >100,000, RoT >30,000 with no bleeding manifestations necessitating platelet enhancing therapy) after the end of the mini-pool IVIG therapy,

7-Study protocol highlights:
Infusion of 1 gm/kg of mini-pool IVIG as a loading dose over 6-8 hours, then repeat every 2-4 weeks as a maintenance dose of 0.5 gm/KG every 2 – 4 weeks according to platelet count at end of 2nd week for 5 subsequent doses
-Age at diagnosis, sex, family history of bleeding
-History of infection or vaccination before thrombocytopenia, onset of bleed acute or insidious onset
- Initial blood count at onset of the diagnosis, at enrollment and before IVIG infusion and 72 hours after end of IVIG infusion
-Repeat CBC:
-Platelet Count Below 50,000/µl repeat CBC weekly
- Platelet Count Above 50,000/µl repeat CBC every 2 weeks
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-Record the following:
-Platelet count 72 hours after infusion, after 2 weeks and just before subsequent maintenance dose
-Infusion related adverse events
-Frequency and site of bleeding episodes according to BAT scoring
-Need for hospitalization
-School attendance
-Physical activities

-Early study termination:

-Severe adverse events
-Non-compliance (missing 2 consecutive visits)
-No improvement in platelet count after 3 infusions (< doubling basal pc or PC <30,000/mm3)

Quality of response
CR: platelet count ≥ 100 × 109/L and absence of bleeding

R: platelet count ≥ 30 × 109/L and at least 2-fold increase the baseline count and absence of bleeding

Time to response: time from starting treatment to time of achievement of CR or R

NR: platelet count < 30 × 109/L or less than 2-fold increase of baseline platelet count or bleeding

Loss of CR or R: platelet count below 100 × 109/L or bleeding (from CR) or below 30 × 109/L or less than 2-fold increase of baseline platelet count or bleeding (from R)

T**iming of assessment of response to IVIG**: monthly for 6 months, bleeding and CBC
Duration of response

- Measured from the achievement of CR or R to loss of CR or R
- Measured as the proportion of the cumulative time spent in CR or R during the period under examination as well as the total time observed from which the proportion is derived [8]

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