Treatment of thromBocytopenia with EltRombopag or Intravenous Immune Globulin (IVIG) Before and DurING Invasive Procedures in Patients with Immune ThrombocytoPenia.

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To compare the effect of eltrombopag and IVIG on the achievement of the platelet count threshold before and after surgery.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Platelet disorders
Study type	Interventional

Summary

ID

NL-OMON46896

Source
ToetsingOnline

Brief title
BRIDGING ITP Study

Condition

- Platelet disorders
- Autoimmune disorders

Synonym
Immune trombocytopenia, ITP

Research involving
Human

Sponsors and support

Primary sponsor: HagaZiekenhuis
Source(s) of monetary or material Support: Hagaziekenhuis

Intervention

Keyword: Eltrombopag, Immune trombocytopenia, IVIG, Pre-operative

Outcome measures

Primary outcome

Proportion of patients achieving the platelet count threshold before surgery

and maintaining platelet counts within the

target range until 7 days after surgical hemostasis is achieved without the use

of ITP rescue treatment.

Secondary outcome

- Time to treatment failure;

- Bleeding;

- Proportion of patients who undergo surgery as planned;

- Treatment satisfaction assessed on Day -1 +/-1 day and once

during follow up using the Treatment Satisfaction

Questionnaire for Medications Score (which incorporates

effectiveness, convenience, side effects, and overall

satisfaction);

- Proportion of patients who have a platelet count greater than

400x109/L during the pre- and post-operative period;

- Use of blood transfusions (platelets, red blood cells, plasma);

- Pre-surgery platelet count levels;

- Change in pre-surgery platelet count levels from baseline;

- Proportion of post-surgery days spent below the platelet

count threshold [50x 109/L (for minor surgery); 100x 109/L (for

major surgery)] during the study period;

- Total clinic and hospital days;

- Venous thromboembolism and arterial thromboembolism;

- Adverse events.

Study description

Background summary

Immune thrombocytopenia (ITP) is a heterogeneous autoimmune disease characterized by the presence of platelet autoantibodies, low platelet counts and an increased risk of bleeding. The clinical presentation of ITP can range from asymptomatic thrombocytopenia to serious hemorrhage. Many patients with moderate to severe ITP (platelet count less than 50 x 109/L) have stable platelet counts and do not bleed; however, when surgeries or invasive procedures become necessary, additional treatment is often required to increase the platelet count to achieve adequate hemostasis. Although specific guidelines for surgical platelet count thresholds in ITP are lacking, platelet transfusion guidelines recommend a platelet count of 50 - 100 x109/L for the vast majority of surgical procedure; 50x109/L is a typical threshold for minor surgeries like tooth extractions and endoscopies; and 100x109/L is used for major surgery like cardiac surgery or neurosurgery. In preparation for this trial,we met with ITP physicians across Canada and investigators on this trial to reach consensus about platelet count thresholds that would be acceptable and feasible for this ITP bridging study. Investigators agreed that thresholds of 50 x109/L for minor surgeries and 100 x109/L for major surgeries were acceptable and reflected most patterns of practice.

Commonly, intravenous immunoglobulin (IVIG) is used to rapidly increase platelet counts in ITP patients before an invasive procedure. IVIG is associated with a transient platelet count response in approximately 80% of patients, which occurs within 2 * 4 days. In most patients, platelet counts remain elevated for approximately 4 weeks, allowing enough time to complete the procedure and for adequate post-operative hemostasis. The use of IVIG as bridging therapy has several disadvantages. First, it is a blood product and

thus carries a theoretical risk of infectious disease transmission. Second, it is associated with side effects. Common side effects include headache (approximately 10%) which can be severe and require hospitalization for 1 * 2% of patients. Hemolysis occurs in approximately 1.6% of treated patients and is most often an effect of high titre anti-A or anti-B in the IVIG product. Rare thromboembolic complications of IVIG including venous (deep vein thrombosis and pulmonary embolism) and arterial thrombosis (myocardial infarction, stroke) have been reported in approximately 1% of treated patients. Renal failure can occur rarely and may be related to sucrose induced osmotic nephropathy. Thus monitoring for these complications is required particularly in elderly patients, diabetics and patients with pre-existing renal insufficiency. Third, IVIG is resourceintensive requiring 0.5 * 1.0 clinic days for the administration of one intravenous dose which is often repeated, the use of outpatient hospital services and nursing time. Finally, IVIG is expensive and supply-limited with a high and increasing per capita cost in Canada. Alternatives to IVIG as bridging therapy are needed.

Based on the results from Phase III studies, eltrombopag can elevate and sustain platelet counts in a significant percentage of ITP patients receiving continuous treatment. These studies also showed that adverse events associated with eltrombopag therapy are uncommon compared to patients receiving placebo. Thus, considering the cost of eltrombopag and the good safety profile, the short-term use of eltrombopag as a bridge to surgery is appealing and may offer a preferable alternative to IVIG for patients with ITP.

Study objective

To compare the effect of eltrombopag and IVIG on the achievement of the platelet count threshold before and after surgery.

Study design

Randomized, open label, parallel arm, non-inferiority trial

Intervention

Eltrombopag daily oral drug for bridging to an acceptabel level of platelet count vs. IVIG in ITP patients.

Study burden and risks

Participating subjects will have to visit the doctor more often and get 2 extra venapunctions for control of plateletcount before and after surgery. They need to fill a short satisfaction questionnaire twice. Patient randomized to the eltrombopag arm will have less burden of getting IVIG, since eltrombopag is an orally taken drug.

Group relatedness is not applicable in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Primary or secondary ITP (according to the ASH 2011 guidelines);
2. Platelet count below the surgical platelet count threshold (50 x109/L for minor surgery; 100
x 109/L for major surgery);
3. 18 years of age or older;
4. On stable doses of concomitant ITP medications (or no medication) for at least 2 weeks (i.e. the dose administered has not changed);
5. At least 3-weeks lead time available between randomization and scheduled surgery;
6. IVIG and Eltrombopag are acceptable ITP treatment options for this patient;

7. Able to provide informed consent.

Exclusion criteria

1. Pregnancy or breastfeeding;
2. Treatment with IVIG within the last 2 weeks;
3. Treatment with a thrombopoietin receptor agonist (eltrombopag or romiplostim) within the last 4 weeks;
4. AST, ALT above 2X upper limit of normal;
5. Bilirubin above 1.5X upper limit of normal in the absence of clinically benign liver disorder (e.g. Gilberts syndrome);
6. Deep vein thrombosis, myocardial infarction, thrombotic stroke or arterial thrombosis in the
last 12 months;
7. History of bone marrow reticulin or fibrosis;
8. Known liver cirrhosis;
9. Active malignancy (defined as requiring treatment or palliation within the last 6 months).
10. Any additional laboratory test result, health related illness or other diagnosis which, in the opinion of the treating physician, may put the subject's health or safety at risk.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	IVIG
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Revolade
Generic name:	Eltrombopag
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-01-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	10-04-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-004295-22-NL
ClinicalTrials.gov	NCT01621204
CCMO	NL59645.098.16