Efficacy and Safety of Eltrombopag + CSA in Patients With Moderate Aplastic Anemia (EMAA) (EMAA)

This study is currently recruiting participants. (see Contacts and Locations)

Verified February 2016 by University of Ulm

Sponsor:
B. Höchsmann

Information provided by (Responsible Party):
B. Höchsmann, University of Ulm

ClinicalTrials.gov Identifier:
NCT02773225

First received: February 29, 2016
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History of Changes

Purpose

The aim of this study is to improve treatment of Moderate Aplastic Anemia (MAA) by evaluating the safety and efficiency of Eltrombopag as a new treatment option in patients with therapy requiring MAA.

Condition	Intervention	Phase
Anemia, Aplastic	Drug: Eltrombopag Drug: Placebo (for Eltrombopag)	Phase 2 Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: Efficacy and Safety of Thrombopoetin-Receptor Agonist Eltrombopag in in Combination With Ciclosporin A in Moderate Aplastic Anemia (**EMAA**): Prospective Randomized Multicenter Study

Resource links provided by NLM:

MedlinePlus related topics: Anemia Aplastic Anemia

Drug Information available for: Cyclosporine Eltrombopag

Genetic and Rare Diseases Information Center resources: Aplastic Anemia

U.S. FDA Resources

Further study details as provided by University of Ulm:

Primary Outcome Measures:

- Trilineage hematologic response rate (CR + PR) [Time Frame: 6 months after treatment start] [Designated as safety issue: No]

  The primary objective of this trial is to investigate whether Eltrombopag added to standard immunosuppressive treatment increases the rate of hematologic responses (complete and partial response) in untreated AA patient at six months after treatment start. A complete response (according to Marsh et al Blood 1992): A peripheral blood count with an ANC > 2.0 G/L and a platelet count > 100 G/L and transfusion independence. A partial response (according to Marsh et al Blood 1992): A peripheral blood count with an ANC >1.0 G/L and a platelet count >30 G/L and transfusion independence Transfusion independence is defined as No need for platelet transfusions in the last 4 weeks prior to evaluation and no need for packed red blood cell concentrates (PRBC) in the last 6 weeks prior to evaluation. Patients who remain transfusion-dependent will be classified as non-responders regardless of the ANC and platelet count.

Secondary Outcome Measures:

- Trilineage hematological response rate (CR and PR, detailed definition => primary endpoint) at 3, 12 and 18 [Time Frame: 3, 12 and 18 months] [Designated as safety issue: No]

  Increase of the platelet count by 20 G/L or hemoglobin by > 1.5 g/dL above baseline in patients without prior transfusion dependence or an absolute increase in ANC of > 0.5 G/L respectively at least a 100 percent increase over the baseline ANC in those with pre-treatment absolute ANC of ≤ 0.5 G/L or transfusion independence for a minimum of 8 weeks or a reduction of transfused units during the last 8 weeks compared with the 8 weeks previous to study entry in patients with prior transfusion dependency

- single hematological response rate (CR and PR, detailed definition => primary endpoint) at 3, 12 and 18 [Time Frame: 3, 12 and 18 months] [Designated as safety issue: No]

  Increase of the platelet count by 20 G/L or hemoglobin by > 1.5 g/dL above baseline in patients without prior transfusion dependence or an absolute increase in ANC of > 0.5 G/L respectively at least a 100 percent increase over the baseline ANC in those with pre-treatment absolute ANC of ≤ 0.5 G/L

- cumulative incidence of response [Time Frame: 3, 6, 12 and 18 months] [Designated as safety issue: No]

  proportion of patients with need for transfusions and number of units transfused (PRBC and platelet concentrates) since start of treatment cumulative incidence of progress to SAA/VSAA or intensive immunosuppressive treatment with ATG

- Comparison of number of SAEs between the two arms (CSA + Placebo versus CSA + Eltrombopag [Time Frame: 2 years] [Designated as safety issue: Yes]

  using the CTCAE criteria and the study specific criteria (developing of a ALT > 3.0 × ULN combined with an elevation of bilirubine > 2.0 × ULN, thrombotic/thromboembolic complications, clonal evolution)

Estimated Enrollment:	116
Study Start Date:	March 2015
Estimated Study Completion Date:	September 2021
Estimated Primary Completion Date:	September 2020 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Eltrombopag + Ciclosporin A Eltrombopag, 75 mg film tablets, starting dose: 2 tablets (150 mg per day), daily, per os + According to European guidelines CSA is administered orally with an initial daily dose of 5 mg/kg/day divided into two doses. Then dosage should be adjusted with the aim of a trough CSA blood level of 200–400 ng/mL (using a polyclonal assay) or 150–250 ng/mL (using a monoclonal assay).	Drug: Eltrombopag • CSA + Eltrombopag, evaluation after three month therapy start regarding dose escalation • 6 month after therapy start --> evaluation and report of remission status of the study office --> unblinding by study office --> partial or complete remission Eltrombopag and slow tapering of CSA • 12 month after therapy start --> evaluation and report of remission status --> complete and partial remission --> tapering/end of study treatment Other Name: Experimental arm
Placebo Comparator: Placebo + Ciclosporin A Placebo for Eltrombopag 75 mg film tablets, 2 tablets, daily, per os + According to European guidelines CSA is administered orally with an initial daily dose of 5 mg/kg/day divided into two doses. Then dosage should be adjusted with the aim of a trough CSA blood level of 200–400 ng/mL (using a polyclonal assay) or 150–250 ng/mL (using a monoclonal assay).	Drug: Placebo (for Eltrombopag) • CSA + Placebo, evaluation after three month therapy start regarding dose escalation • 6 month after therapy start --> evaluation and report of remission status of the study office --> unblinding by study office --> no complete remission: CSA + Eltrombopag and evaluation 3 months after therapy start --> dose escalation • 12 month after start of eltrombopag --> evaluation and report of remission status --> complete and partial remission --> tapering/end of study treatment Other Name: control

Detailed Description:

After enrollment (see detailed inclusion and exclusion criteria below) the patients are randomized either to the Placebo or Eltrombopag arm. The randomization is double blinded. Randomization will take in account patient's age and disease severity by stratifying into 4 block combinations to ensure homogeneity between treatment arms. All patients receive background therapy with CSA, regardless of randomisation group, to treat MAA according to current standard of care.

Eltrombopag (or Placebo) is given at a daily starting dose of 150 mg orally as 75 mg tablets once daily (2 tablets Eltrombopag or placebo per day), (Olnes et al NEJM 2012).

In Asian patients Eltrombopag (or Placebo) is given at a daily starting dose of 75 mg orally (1 tablet Eltrombopag or placebo per day). In Asian-Caucasian patients no dose reduction of the starting dose is carried out, but cautious observation of the liver function due to the possibility of altered Eltrombopag metabolism is recommended.

Dose reduction:

In patients without history of thromboembolism or known risk factors for thrombembolism dose reduction (the possibility of an alternating dose schedule is given) is recommended if the platelet count is increasing > 150 G/L.

- Dosage should be decreased to achieve a platelet count between 100 and 150 G/L after reaching a sufficient erythrocyte and granulocyte response (see 10.1).
- If the platelet count decreases below 100 G/L the Eltrombopag dose should be escalated again.
- Eltrombopag should be discontinued if the platelet count exceeds 450 G/L and could be restarted with a lower dose after decrease of the platelet count below 150 G/L.

In patients with history of thromboembolism or known risk factors for thromboembolism (e. g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, PNH with GPI-deficient granulocyte population > 50 %, prolonged periods of immobilization, contraceptives and hormone replacement therapy or surgery) dose reduction is recommended if the platelet count is increasing > 100 G/L

- The target platelet count will be 70-120 G/L after reaching a sufficient erythrocyte and granulocyte response (see 10.1).
- If the platelet count decreases below 70 G/L the Eltrombopag dose should be escalated again.
- Eltrombopag should be discontinued in patients with history of and risk factors for thromboembolism if the platelet count exceeds 150 G/L.

Duration of follow up: Last Follow up 24 months after end of study treatment. Patients will receive Eltrombopag or placebo within the study for a minimum of 6 months. Exceptions are patients with disease progression in Severe or Very Severe AA or patients with inacceptable adverse events within the first 6 months.

Eltrombopag will be administered for a maximum period of 12 months within the protocol. Recent data show that the response of hematopoiesis in refractory severe aplastic anemia can be sustained on discontinuation of Eltrombopag25.

As long-term effects of investigational treatments are an objective of the study, the follow-up of patients will cover 24 months after the end of the study treatment according to the protocol

Eligibility

Ages Eligible for Study:	18 Years and older (Adult, Senior)
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. Current diagnosis of a Moderate Aplastic Anemia requiring standard treatment with CSA without prior specific therapy. MAA is defined as Aplastic Anemia fulfilling the following criteria:
   - no evidence for other disease causing marrow failure
   - hypocellular bone marrow for age
   - depression of at least two out of three peripheral blood counts below the normal values:
     - absolute neutrophil count (ANC) < 1.2 G/L and > 0.5 G/l
     - platelet count < 70 G/L
     - absolute reticulocyte count < 60 G/L

   without fulfilling the criteria for SAA (hypocellularity of bone marrow 25 % and depression of two of the three peripheral counts: ANC < 0.5 G/L, platelet count < 20 G/L, reticulocyte count < 20 G/L)
2. In this study need for treatment with CSA is defined as:

2a) transfusion-independent MAA and:

- ANC < 1.0 G/L
- or hemoglobin < 8.5 g/dl and reticulocyte count < 60 G/L
- or platelet count < 30 G/L
- or significant clinical symptoms (infections, bleeding, anemia) 2b) transfusion-dependent moderate aplastic anemia
- Platelet transfusion dependency is defined as prophylactic transfusion (platelet counts < 10 G/L with no bleeding) or therapeutic transfusion in the 12 weeks prior to study entry
- Red cell transfusion dependency is defined as transfusion of at least 4 units of packed red blood cell concentrates (PRBC) in the 12 weeks prior to study entry 3) A signed and dated informed consent is necessary before the conduct of any study-specific procedure.

Exclusion Criteria:

1. Age < 18 years
2. Severe or Very Severe Aplastic Anemia (hypocellularity of bone marrow 25 % and depression of two of the three peripheral counts: ANC < 0.5 G/L, platelet count < 20 G/L, reticulocyte count < 20 G/L)
3. Constitutional aplastic anemia (Fanconi anemia or Dyskeratosis congenita)
4. Clonal myeloid disorders based on cytogenetic findings performed within 12 weeks of study entry. Especially, patients with cytogenetic abnormalities which are recurrent in MDS are not eligible for the study.
5. Bone marrow reticulin fibrosis of grade 3 or greater
6. Severe concurrent diseases precluding the patient's ability to tolerate protocol therapy

7. ALT > 3 times the upper limit of normal if this elevation is progressive, or persistent for 4 weeks, or accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation
8. Infection not adequately responding to appropriate therapy
9. HIV-positivity (patients with Hepatitis B or Hepatits C-positivity are only in combination with hepatic failure (see criteria 7) excluded)
10. Moribund status with a likely death within 3 months
11. History of malignancy other than localized tumors diagnosed more than one year previously and treated surgically with curative intent (for instance squamous cell or other skin cancers, stage 1, breast cancer in situ, cervical carcinoma in situ...).
12. Prior specific treatment of Aplastic Anemia with immunosuppression or androgens or interleukin2-receptor-antibodies. The use of these drugs in context of other disorders before diagnosis of aplastic anemia is not an exclusion criteria if these treatments were finished longer than 6 months before study entry.
13. Treatment with other hematological effective drugs (including erythropoetin) within 3 months before study entry as well as treatment with corticosteroids and G-CSF within 3 weeks before enrollment
14. Known hypersensitivity to Eltrombopag or its components
15. Known hypersensitivity to Ciclosporin
16. Current nursing, pregnancy, or unwillingness to take oral contraceptives or use a barrier method of birth control to refrain from pregnancy as well as a missing or positive pregnancy test within the last 14 days before inclusion for women with childbearing potential during the course of this study.
17. Inability to understand the investigational nature of the study or to give informed consent.
18. Renal failure with creatinine > 2× upper limit of normal.
19. Uncontrolled hypertension
20. Participation in any study using an investigational drug or treatment with an investigational drug within 30 days preceding the first dose of study medication

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02773225

Contacts

Contact: Kiok Kathrin, Dr rer nat Kathrin.kiok@gwtonline.de

Contact: Köhler Carsta, Dr carsta.koehler@gwtonline.de

Locations

Germany

University Hospital Ulm **Recruiting**
Ulm, Germany, 89081
Contact: Britta Höchsmann, MD hoechsmann@blutspende.de

Sponsors and Collaborators

B. Höchsmann

Investigators

Principal Investigator: Britta Höchsmann, MD Sponsor GmbH

More Information

Responsible Party:	B. Höchsmann, Dr. med., University of Ulm
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Other Study ID Numbers:	9345
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Individual Participant Data Plan to Share IPD:	Yes

Keywords provided by University of Ulm:
non severe Aplastic Anemia,

Additional relevant MeSH terms:

Anemia	Immunosuppressive Agents
Anemia, Aplastic	Immunologic Factors

Hematologic Diseases
Bone Marrow Diseases
Cyclosporins
Cyclosporine
Enzyme Inhibitors
Molecular Mechanisms of Pharmacological Action
Physiological Effects of Drugs
Antifungal Agents
Anti-Infective Agents
Dermatologic Agents
Antirheumatic Agents
Calcineurin Inhibitors

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