A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON44180

Source
ToetsingOnline

Brief title
RACE

Condition

- Haematological disorders NEC

Synonym
panmyelopathy; bonemarrow failure

Research involving

Human

Sponsors and support

Primary sponsor: European society for Blood and Marrow Transplantation
Source(s) of monetary or material Support: Alexion Pharmaceuticals,Novartis,Novartis;Pfizer en Alexion,Pfizer

Intervention

Keyword: Eltrombopag, horse antithymocyte globuline (hATG), Immunosuppression Therapy (IST), Severe Aplastic Anemia (SAA)

Outcome measures

Primary outcome

Rate of Complete response (defined as Hb >10 g/dL, ANC > 1,000/*L and Plt >100,000 *L) at 3 months since start of treatment in untreated severe AA patients.

Secondary outcome

1. Time to first hematological response (complete or partial) described by a cumulative incidence curve (see paragraph 9.6)

2. Time to best hematological response, described by a cumulative incidence curve (see paragraph 9.6)

3. Time to complete response (see paragraph 9.6)

4. Rates of hematological response (overall, complete, partial) at 6, 12, 18 and 24 months

5. Overall survival (OS) probability; OS is defined as time from treatment starting (day 1) to death, or last follow-up for patients alive

6. Event-free survival (EFS) probability; EFS is defined as time from treatment starting to either relapse, death, treatment failure or clonal evolution

(whichever occurs first), or last follow-up for patients alive in response

7. Cumulative incidence of relapse, from first hematological response (complete or partial) (see paragraph 9.6)

8. Cumulative incidence of clonal evolution (as defined below, see 9.5): AML, MDS or karyotypic abnormalities (see paragraph 9.6)

9. Cumulative incidence of PNH population occurrence and clinical hemolytic PNH occurrence (see paragraph 9.6)

10. Cumulative incidence of discontinuation of immunosuppressive therapy

11. Rate of CsA-independent hematological response at 24 months

12. Need for transfusions (packed red cell units and platelet units) and number of transfusions required from treatment.

13. Need for any supportive care, including hospitalization

14. Quality of life (as assessed by the validated EORTC QLQ-C30 questionnaire)(changes over time and differences between treatment arms)

15. Safety and tolerability of the investigational treatment, including SAE

Study description

Background summary

Severe aplastic anemia (SAA) is an hematological disease of the bone marrow resulting in an impairment of the production of blood cells. As a result of this disease you are suffering from a lack of all blood cells, possibly leading to clinical sign and symptoms that may affect your well-being, and may result in medical complications. Aplastic anemia, especially in its severe form, is considered a life-threatening disease. Thus, patients diagnosed with SAA require a prompt and adequate treatment which aims to restore the functioning of the bone marrow, and thus to reduce the risk of potentially fatal complications.

The current standard IST for SAA is based on the association of anti-thymocyte globulin (ATG) and cyclosporine A (CsA). It is well demonstrated that this treatment may result in clinical response in about two thirds of patients, with improvement of blood counts beginning around 3 months from the treatment start, and possibly further improving over time. Recent data have demonstrated that one specific type of ATG (horse-ATG, commercial brand ATGAM from Pfizer) seems superior to the other commercially available ATGs, and thus ATGAM, is currently the recommended preferred ATG for front-line IST in SAA. However, all patients should continue maintenance IST with CsA for at least 12 months, possibly tapered very slowly in the subsequent months, even if irrespective of this long-term maintenance IST about one third of patient may relapse.

Recently, a new drug, eltrombopag, has been investigated for the treatment of SAA. eltrombopag, is a compound which stimulates the functioning of the bone marrow independently from IST. It has recently been demonstrated that eltrombopag has a positive effect as well on the blood cell production.

Study hypothesis: that the experimental treatment will increase the 3 months response rate up to 21% (by 3 folds, based on the 7%expected in the control groups at 3 months after treatment start.

Study objective

The objective of this trial is to investigate whether Eltrombopag added to standard immunosuppressive treatment increases the rate of early (at three months) complete response and blood counts and can be use as front-line therapy for SAA treatment.

Study design

Prospective, randomized, multi-center phase III study.

Intervention

Two treatment arms, A and B, where subjects randomisized to arm A will receive the standard treatment for SAA (hATG+CsA) whereas subjects randomized to arm B will receive the experimental treatment (hATG+CsA+eltrombopag).

Study burden and risks

The persons who are approached by their treating physician for possible participation in the RACE trial are diagnosed with severe aplastic anemia and are not eligible for a bone marrow transplant.I
If they decide to participate in this study, they are assured that they will receive the, at the moment, best possible treatment for SAA (standard treatment). This treatment is exactly the same as the treatment that SAA

patients will receive who do not participate in the RACE study. participation in this study not only offers patients the best treatment for SAA, but also the possibility of receiving the standard treatment + a drug which has proven to stimulate the bone marrow function.

The treatments have side effects such as nausea, headache, increased blood pressure and reduction of kidney- and liver function. The side effects of CsA are related to increased CsA dose and will therefore be closely monitored to prevent overdose. ATGAM may, due to its immunesuppressing pharmacological effect, theoretically lead to an increased risk of infections.
For both drug belonging to the standard treatment, it is accounted that the subject will experience the same side effects when they decide not to participate in this study because the standard treatment is equal to the SAA treatment that patients receive outside of the protocol.

Eltrombopag is generally well tolerated and it has shown an acceptable toxicity profile. The most common toxicity of eltrombopag pertains to the liver, with mild to moderate increase of liver testings; for this reasons your biochemical parameters will be accurately monitored during the study. Nausea, vomiting, headache are other common adverse events, whereas thromboembolic events are possible but eventually associated with high platelet counts. Changes can occur in blood and bone marrow, which can lead to the development of cancer. Patients will be checked during the study on this changes.

After inclusion of the subject in the study there will be a screening visit to ensure that the subject is eligible to participate in the study (Pregnancy test, DEB test). There will be additionally tests performed, next to the standard SAA diagnosis and physical examination, including: bone marrow aspirate and biopsy and blood draws. Bone marrow biopsies will be performed at 3 additional visits (6 months; 12 months; and 24 months). If the patient is in CR at 3 months, this will be confirmed by an additional bone marrow biopsy. Especially the bone marrow biopsies may be experienced as painful by the patient. However, this treatment is part of the standard treatment of SAA patients outside this study.

There will be 22 visits in total during two years of the study. During these visits blood is drawn from the subject. This is standard for SAA treatment but the amount of visits is higher when taking part in this study. The volume of blood drawn from the subject shall thus be higher, as well for additional testing (genetically) to provide better insights in SAA and to monitor the treatment progression. The subject has given consent for these additional samples before inclusion in the study

On four different timepoints during the study (screening visit,6 months, 12 months, 24 months) the subject will be asked to complete a "quality of life" questionnaire. Questions cover global health status, physical, emotional and social well being, pain and financial difficulties due to treatment or disease.

This questionnaire may be experienced as emotionally hard since the subject is confronted with his or her disease (SAA).

Possibly, the subject experiences a disappointment when he or she is randomized in the standard treatment arm or when there is no complete response after treatment with eltrombopag.
In case that the subject is randomized in treatment arm A (standard treatment arm) and there has been no signs of complete response after 6 months, then this subject will be eligible to receive a treatment with eltrombopag, outside of the protocol. In the case of relapse or partial response to treatment after 3 months of a subject randomized in treatment arm B (experimental arm), a second round of treatment with eltrombopag will be started.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

1.Diagnosis of severe or very severe aplastic anemia, defined by ;* At least two of the following:;* Absolute neutrophil counts <0.5 x 10(9)/L (severe) or ;<0.2 x 10(9)/L (very severe);* Platelet counts <20 x 10(9)/L;* Reticulocyte counts <60 x 10(9)/L;* Hypocellular bone marrow (<30% cellularity), without evidences of fibrosis or malignant cells;2.Age * 15 years;;3.Written informed consent;4. Willing and able to comply with all of the requirements and visits in the protocol;5. Understands that they can be randomised to either treatment arm;6. Negative pregnancy test for women of child bearing age;7. Written acceptance to use contraception (hormonal or barrier method of birth control; abstinence) for the entire duration of study participation.

Exclusion criteria

1.Prior immunosuppressive therapy with ATG (horse of rabbit) or any other lymphocyte depleting agent (i.e., alemtuzumab);2.Eligibility to a sibling allogeneic stem cell transplantation ;3.Evidence of a myelodysplastic syndrome, defined by the presence of myelodysplastic features, excess of blasts or karyotypic abnormalities typical of MDS (according to revised WHO 2008 ;criteria) , as well as other primitive marrow disease. Patients with diagnosis of AA with cytogenetic abnormalities which are recurrent in MDS (according to revised WHO 2008 criteria) should be included in this category, and are not eligible for the study; patients with del(20q), +8 and *Y are not included in this category, and thus are eligible for this study. The list of karyotypic abnormalities which qualifies for the diagnosis of MDS are listed in the Appendix 1.;4.History or clinical suspect of constitutional aplastic anemia (i.e. Fanconi Anemia with positive DEB/MMC test or Dyskeratosis Congenita) ;5.History of malignant tumors with active disease within 5 years from enrollment and/or previous chemo-rediotherapy;6.Previous history of stem cell transplantation;7.Treatment with cyclosporin A; <4 weeks of cyclosporin A treatment before enrollment, wash out period of 2 weeks before enrollment;8.CMV viremia, as defined by positive PCR or pp65 test;9.WHO performance status *3;10.Pregnant or breast feeding patients;11.Patients with hepatic, renal or cardiac failure, or any other life-;threatening concurrent disease;12.Patients with HIV infection;13.Patients without social health care assistance;14.Participation in another clinical trial within 1 month before the start of this trial;15.Subjects with known hypersensitivity to any of the component medications

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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-02-2016
Enrollment:	48
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	01-09-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	07-01-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	28-06-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	12-12-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	27-02-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	13-12-2018
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	EUCTR2014-000363-40-NL
ClinicalTrials.gov	NCT02099747
CCMO	NL50426.058.15