A Phase I/II study to determine the safety and efficacy of a combination of anti-CD3 & anti-CD7 ricin A immunotoxins for treating steroid-resistant acute graft-versus-host disease.

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PRIMARY• To determine the efficacy on study Day 28 of the IT-combination in inducing a clinical response in patients with severe acute GVHD refractory to first line therapy with intermediate dose corticosteroids. SECONDARY• To evaluate the overall...

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

Summary

ID

NL-OMON31737

Source
ToetsingOnline

Brief title
IT-combination for aGVHD

Condition

- Other condition

Synonym
acute graft-versus-host disease, GVHD

Health condition

Immuunsysteemaandoeningen: acute omgekeerde afstotingsziekte

Research involving
Human

Sponsors and support

Primary sponsor: Henogen S.A.
Source(s) of monetary or material Support: Ministerie van OC&W,An attempt will be made to obtain some R&D grants,Contribution of the Sponsor

Intervention

Keyword: acute Graft-versus-Host Disease, hematopoietic stem cell transplantation, immunotoxin, steroid resistant

Outcome measures

Primary outcome

PRIMARY

• The acute GVHD response rate on study Day 28.

Secondary outcome

SECONDARY

• The safety and tolerability of the IT-combination, as determined by the

number and intensity of adverse and serious adverse events during 12 months.

• The acute GVHD relapse rate.

• The incidence of chronic GVHD during 12 months.

• The overall survival and progression free survival during 12 months.

• The kinetics of treatment-induced T cell and NK cell depletion.

• The pharmacokinetic profile of the IT-combination.

• The occurrence and extent of humoral responses against the IT-combination.

• The occurrence of treatment-induced cytokine release, as determined by the measurement of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, and IFN-γ plasma levels at t = 0 (pre-dose), 1, and 4 hours after the start of each infusion.

ADDITIONAL RESEARCH

• The composition and the evolution of the T-, B- and NK-cell compartments at pre-treatment and at Day 28, 3, 6, and 12 months as determined by flow cytometry.

• The composition and the evolution of the T-cell receptor (TCR)-repertoire at pre-treatment and at Day 28, 3, 6, and 12 months.

• The identification and evolution of host-reactive T-cell clones at pre-treatment and at Day 28, 3, 6, and 12 months.

• The monitoring of gene expression patterns associated with success/failure of host-tolerance at pre-treatment and at Day 28, 3, 6, and 12 months.

• The monitoring of the frequency of host-specific cytotoxic T cells in the patients peripheral blood at Day 28, 3, 6, and 12 months.

• The monitoring of the number of EBV/CMV virus-specific T cells and the EBV/CMV viral load at pre-treatment and at Day 28, 3, 6, and 12 months.

Study description

Background summary

Acute GVHD is a feared and often life-threatening complication of allogeneic hematopoietic stem cell transplantation. Acute GVHD is caused by donor-derived T-cells that are co-transplanted with the graft and that recognize tissues of their new host as *foreign*. Moreover, acute GVHD may also occur in patients that are given post-transplant donor lymphocyte infusions (DLI) to prevent/treat the recurrence of the underlying malignant disease. In vivo elimination of the mature (mostly donor-derived) T cells in the patient can be used as treatment of the disease, and allows the restoration of the T-cell compartment with newly formed T cells. As these will now grow up in their new environment, the recipient is likely to be accepted as *self* (*resetting* of the T-cell compartment).

In this study, a combination of two T-cell directed antibodies both conjugated to a cell-killing toxin will be evaluated. Previous in vitro studies have demonstrated that this so-called immunotoxin-combination (IT-combination) acts synergistically in eliminating T cells. In a subsequent clinical pilot-study, the IT-combination has generated encouraging results when applied as third line therapy. Extensive biological and clinical responses could be noted in the absence of severe acute toxicities. Building on this experience, the current study aims at evaluating the characteristics of the IT-combination when administered in an earlier phase of the disease, i.e. as second line instead of as third line therapy.

Study objective

PRIMARY
• To determine the efficacy on study Day 28 of the IT-combination in inducing a clinical response in patients with severe acute GVHD refractory to first line therapy with intermediate dose corticosteroids.

SECONDARY
• To evaluate the overall safety and efficacy during the first 12 months after initiation of therapy.

• To determine the pharmacokinetic profile of the IT-combination.

• To determine the immunogenicity of the IT-combination.

ADDITIONAL RESEARCH
• The patient will be asked to participate in additional research aiming at determining the presence and evolution of biomarkers suggestive for the extent to which the IT-combination *resets the T-cell compartment*, induces tolerance, and/or enhances the risk of over-immunosuppression.

Study design

• The experimental design is a non-controlled multicentric fixed-dose Phase I/II study.

• The treatment consists of a standard dose of 4 infusions IT-combination (4 mg/m2), given 48-hours apart over a 4-hour period.

• In case Dose Limiting Toxicities (DLT) are encountered, a downward dose modification scheme based on the conventional *3+3 design* will be applied (Paragraph 6.6 study protocol). The maximal tolerable dose (MTD) is defined as the highest dose at which DLT occur in less than 33% of the patients.

• For the second and subsequent patients to be treated at this standard dose level, it is required that the previous patient have been observed for at least 48 hours after the last infusion, and the maximal tolerable dose has not been reached.

• A total of 12 evaluable patients will be enrolled in 4 transplant centers throughout the Netherlands, in a 9 to 12 months period.

• The intended follow-up period is 12 months.

Intervention

A treatment course consists of four doses of IT-combination, given 48-hours apart as a 100 ml intravenous infusion over a 4-hour period.

Study burden and risks

The main dose limiting toxicities associated with similar products have been vascular leak syndrome and myalgia associated with elevated serum creatine kinase (CK) levels. Administration of xenogeneic proteins in general may lead to anaphylactic reactions. The systemic administration of anti-CD3 antibodies, as also present in the IT-combination, may result in the activation of T-cells leading to serious cytokine release syndrome. The elimination of T-cells and NK-cells as such (being the effector mechanism of the IT-combination), may render patients more vulnerable to infections and secondary malignancies (e.g. post-transplant lymphoproliferative disorder PTLD).

The observation that the IT-combination, when applied as third-line therapy, generated clear biological and clinical responses without inducing severe acute toxicities, justifies the expectation that patients with less advance disease will also benefit from this agent. Presumably, the immune system and vital organs of such patients will not yet be irreversibly damaged by the aGHVD and immunosuppressive treatment at time of inclusion. Hence, it might be expected that this Phase I/II study generates a significant fraction of responders, hopefully with good long-term prognosis.

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

Patients suffering from severe acute GVHD (Grade II-IV) that is progressing after 3 days, or non-improving after 5 days, of prednisolone at 2 mg/kg a day.

Exclusion criteria

Patients receiving concomitant investigational therapeutics for acute GVHD, including agents used for GVHD prophylaxis, at the time of enrollment.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-05-2008
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	A mixture of anti-CD3 mAb (SPV-T3a)-ricin A chain fusion protein and anti-CD7 mAb (WT1)-ricin A chai
Generic name:	The IT-combination

Ethics review

Approved WMO Date:	21-04-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2007-005467-97-NL
ClinicalTrials.gov	NCT00640497
CCMO	NL14386.091.08