ISRCTN32763606 https://doi.org/10.1186/ISRCTN32763606

Receptor for Hyaluronan-Mediated Motility (RHAMM [CD168]) peptide vaccination for patients with haematological malignancies: a phaseI/II pilot study

Submission date 30/10/2007	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 31/10/2007	**Overall study status** Completed	
Last Edited 24/05/2019	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
N/A

Study information

Scientific Title
Receptor for Hyaluronan-Mediated Motility (RHAMM [CD168]) peptide vaccination for patients with haematological malignancies: a phaseI/II pilot study

Acronym
RHAMM peptide vaccination

Study objectives
Primary study aim:
Proof of the safety and feasibility of a vaccination with this particular peptide in patients with haematological malignancies.

Primary endpoint:
1. Frequency of Severe Adverse Events (SAE)
2. Severity of SAE
3. Timepoints and correlations to the study medication of the SAE

Secondary aims of the study:
1. Induction of a specific T cell immune reponse to RHAMM/CD168
2. Assessment of the influence of the peptide vaccination on the remission status of the present haematological malignancy

Secondary endpoints:
1. Frequency of RHAMM specific T Lymphocytes
2. Remission criteria

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from the Ethics committee of the University of Ulm (Germany) on the 24th September 2004 (ref: UL-RHAMM-1).

Study design
Interventional, non-randomised, non-controlled, pilot study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute Myeloid Leukaemia (AML), Myelodysplastic Syndrome (MDS) or Multiple Myeloma (MM)

Interventions
300 µg RHAMM R3 peptide emulsified with the incomplete Freund's adjuvant on day 3 as well as Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) on days 1 - 5 was administered four times subcutaneously at a biweekly interval.

Timepoints:
Pre examination: week 0
RHAMM-R3 vaccinations: weeks 1,3,5,7 with intermediate examinations
Final examination: week 10

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Receptor for Hyaluronan-Mediated Motility (RHAMM [CD168]) peptide, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

Primary outcome(s)
For all patients the BM blood was analysed before and after vaccination using microscopy and standard Fluorescence Activated Cell Sorter (FACS) analysis. Patients with MM were also examined for quantitative immunoglobulins and quantitative free light chains in serum and urine. The frequency of erythrocyte and platelet transfusions and the course of differential blood count were documented.

Response criteria were as following:
For patients with AML, the criteria by the World Health Organization (WHO) and the International Working Group (IWG) were followed as specified:
Complete Response (CR): reduction of blasts in the BM blood to less than 5%, in peripheral blood count: haemoglobin greater than 11 g/dl, neutrophils 1,500/mm^3 or more, platelets 100,000/mm^3 or more
Partial Response (PR): reduction of blasts in the BM blood of more than 50%, in peripheral blood count: haemoglobin greater than 11 g/dl, neutrophils 1500/mm^3 or more, platelets 100,000 /mm^3 or more
Stable Disease (SD): no CR or PR
Progressive Disease (PD): increase of blasts in the BM blood by more than 50% or increase of WHO-classification or progress of transfusion requirements

For patients with MDS, the criteria by the WHO and the IWG were followed as specified:
CR: a complete response was defined as a normocellular with less than 5% blasts with normal maturation of all cell lines, with no evidence of dysplasia, in peripheral blood count: haemoglobin greater than 11 g/dl, neutrophils 1,500/mm^3 or more, platelets 100,000/mm^3 or more
PR: blasts decreased by 50% or more over treatment or a less MDS WHO classification than pretreatment, Haematological Improvement (HI): an improvement was defined as a decrease of at least of 50% in transfusion requirements, together with at least an improvement of one ot two cell lineages of the peripheral cell counts but not enough to qualify for a PR

SD: failure to achieve at least a HI, but no evidence of progression for at least two months
PD: increase of blasts in bone-marrow of more than 50% or increase of WHO-classification or progress of transfusion requirements

For patients with MM, the International Uniform Response Criteria according to Durie et. al. were applied:
Stringent Complete Remission (sCR): CR as defined below plus normal free light chain ratio and absence of clonal cells in the BM by immunohistochemistry or immunofluorescence
CR: negative immunofixation in the serum and urine
Very Good Partial Response (VGPR): serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein less than 100 mg per 24 hours
PR: greater than or equal to 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by greater than or equal to 90% or to less than 200 mg per 24 hours
SD: no CR or PR
PD: increase of free light chains in serum or urine or of clonal plasma cells in bone-marrow of more than 25%

Key secondary outcome(s))

1. Assessment of toxicity of R3-peptide vaccination:
Side effects were documented according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Before and three weeks after the fourth vaccination physical examination, body weight, ECOG performance score, laboratory tests (kidney and liver function tests, electrophoresis, electrolytes, C-Reactive Protein [CRP], Lactate Dehydrogenase [LDH], and coagulation tests), chest x-ray, echocardiography, electrocardiography, urine analysis, abdominal sonography and bone-marrow aspiration was performed. For patients with MM additionally quantitative immunoglobulins and quantitative assessment of free light chains in serum and urine were tested. Before each vaccination physical examination, laboratory tests (White Blood Cell [WBC] count, differential blood count, kidney and liver function tests, electrolytes, CRP, LDH, coagulation tests and urine analysis) were performed. To detect autoimmune reactions, we measured Thyroid Stimulating Hormone (TSH), free Triiodothyronine (fT3), free Thyroxine (fT4), as well as Antinuclear Antibody (ANA), CRP and Blood Sedimentation rate (BSG).

2. Interferon (IFN)-gamma and Granzyme B Enzyme-Linked Immunosorbent Spot (ELISpot) assays:
IFN-gamma and granzyme B ELISpot assays were performed as previously described to determine specific lysis of RHAMM (peptide) positive target cells according to the manufacturer's instructions (BD, San Diego, USA). We participated in an inter-laboratory test for ELISpot assays.

3. Tetramer staining:
The frequency of R3 specific CD8+ T lymphocytes was determined after eight days Mixed Lymphocyte Peptide Culture (MLPC) by staining with anti-CD8 antibody and HLA-A2/R3 tetramer R-Phycoerythrin (PE). HLA-A2/R3 tetramer PE was synthesised at the Lausanne Branch of the Ludwig Institute for Cancer Research. CD8+ T lymphocytes (0.5 - 1 x 10^6) stimulated with irradiated CD8- Antigen-Presenting Cells (APCs) in the presence of the R3 peptide were stained with HLA-A2/R3 tetramer PE 1 µg per test with respect to the peptide-Major Histocompatibility Complex (MHC) class I component in the dark and incubated for 40 minutes at room temperature. Thereafter, for four-color staining, 10 µl CD8 Peridinin Chlorophyll Protein (PerCP), 10 µl CD45RA Fluorescein Isothiocyanate (FITC) and 4 µl CCR7 APC (BD, Heidelberg, Germany) were added at 4°C for 20 minutes in the dark. As for six-color staining, the cells were stained with 1 µg HLA-A2/R3 tetramer PE and HLA-A2/WT1 tetramer PerCP per test with respect to the

peptide-MHC class I component in the dark and incubated for 40 minutes at room temperature. Thereafter 5 µl CD8 APC-Cy7, 5 µl CD45RA APC (Invitrogen, Caltag, CA, USA), 10 µl CCR7 PE-Cy7, 10 µl CD27 FITC or CD28 FITC (BD, Heidelberg, Germany) were added at 4°C for 20 minutes in the dark. After washing once with Phosphate-Buffered Saline (PBS), stained cells were fixed with 1% formaldehyde (Sigma, Germany) and then analysed by flow cytometry. Whenever possible, at least 100,000 events were collected for analysis. Each sample was run with an appropriate isotype control to define the gate of positive cells. Analysis was performed on tightly gated lymphocytes to exclude dead cells and debris and on CD8+ T lymphocytes to evaluate responses to R3 peptide. Samples were defined as "tetramer positive" in case of an increase of specific R3-tetramer+/CD8+ T cells of more than 50% (if initial count was = 0.1%), or 25% increase (if initial count was greater than 0.1%). We participated in an inter-laboratory test for tetramer flow cytometry assays.

Completion date
01/02/2008

Eligibility

Key inclusion criteria
1. Diagnosis of Acute Myeloid Leukaemia (AML), Myelodysplastic Syndrome (MDS) or Multiple Myeloma (MM)
2. AML: up to 25% blasts in the Bone Marrow (BM); MDS: up to 20% blasts in the BM; MM: partial remission (immunofixation still positive or immunoglobulins still detectable in the urine)
3. Human Leukocyte Antigen A2 (HLA-A2) expression
4. RHAMM-messenger Ribonucleic Acid (mRNA) expression
5. Karnofsky Index greater than or equal to 70 or Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2
6. Aged greater than 18 years
7. At least one cycle of treatment with standard chemotherapy for this haematological malignancy preceding the peptide vaccination
8. Survival time at least 6 months
9. Sufficient renal function (creatinine and Blood Urea Nitrogen [BUN] less than threefold of the upper limit)
10. Sufficient liver function tests (Serum Glutamic Oxaloacetic Transaminase [SGOT]/Serum Glutamic Pyruvic Transaminase [SGPT] threefold of the upper limit)
11. Compliance of the patient
12. Informed consent must be obtained in written form

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex

All

Total final enrolment
10

Key exclusion criteria
1. Allogeneic hematopoietic stem cell transplantation in the history planned
2. Central Nervous System (CNS) involvment, severe psychiatric disease
3. Severe partial or global respiratory failure (New York Heart Association [NYHA] stage greater than or equal to III)
4. Immunosuppressive therapy in the last 4 weeks
5. Pregnancy or breastfeeding
6. Females with no sufficient contraception
7. Contradictions against study therapeuticals (including galenic substances)
8. Severe infections
9. Simultaneous participation in another clinical study trial

Date of first enrolment
01/11/2004

Date of final enrolment
01/02/2008

Locations

Countries of recruitment
Germany

Study participating centre
Universitatsklinikum Ulm
Ulm
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Sponsor information

Organisation
University Hospital Ulm (Universitatsklinikum Ulm) (Germany)

ROR
https://ror.org/05emabm63

Funder(s)

Funder type
Government

Funder Name
This work was supported by generous grants from:

Funder Name
The German José Carreras Leukemia Foundation (Germany)

Funder Name
German Research Council (Deutsche Forschungsgemeinschaft [DFG]) (Germany)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2008		Yes	No