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A randomised, open-label, multicentre, efficacy and safety study examining the effects on viral kinetics of all-trans retinoic acid (Tretinoin) (VESANOID®) in combination with pegylated interferon alpha-2a (PEGASYS®) and ribavirin (COPEGUS®) therapy in patients with genotype 1-chronic hepatitis C and non-response to a previous course of peg-interferon alpha /ribavirin combination (ATRACTION)

Submission date
20/09/2007

Registration date
25/10/2007

Last Edited
10/06/2021

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Clinical Trials Information System (CTIS)
2006-005500-14

Protocol serial number
MZ-ATRACTION ML20804

Study information

Scientific Title
A randomised, open-label, multicentre, efficacy and safety study examining the effects on viral kinetics of all-trans retinoic acid (Tretinoin) (VESANOID®) in combination with pegylated interferon alpha-2a (PEGASYS®) and ribavirin (COPEGUS®) therapy in patients with genotype 1-chronic hepatitis C and non-response to a previous course of peg-interferon alpha/ribavirin combination (ATRACTION)

Acronym
ATRACTION

Study objectives
Effect of all-trans retinoic acid on viral kinetics in non-responder patients with chronic type 1 Hepatitis C Virus (HCV)-infection.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from the Ethics committee of the Landesarztekammer Rheinland-Pfalz on the 4th September 2007.

Primary study design
Interventional

Study design
A randomised, open-label, multicentre, efficacy and safety study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Hepatitis C-Virus infection genotype 1

Interventions
Study medication:
1. All-trans retinoic acid (Tretinoin): 45 mg/m^2 body surface area in 10 mg capsules (roughly corresponding to 8 capsules/day) administered orally (po) daily in split doses (morning/evening twice a day [bid] with meals) for 12 weeks (weeks 1 - 12 in treatment arm A and weeks 13 - 24 in treatment arm B2)
2. Pegylated interferon alpha-2a (40 KD): 180 µg in 0.5 ml solution in a 0.5 ml prefilled syringe

administered subcutaneously (sc) once weekly for 48 weeks (treatment arms A and B1) or for 60 weeks (treatment arm B2)
3. Ribavirin: 1000 - 1200 mg according to patient's body weight at baseline (BL) (1000 mg for patients weighing less than 75 kg and 1200 mg for patients weighing greater than 75 kg) in 200 mg tablets administered po daily, in split doses (morning/evening); each 2 - 3 tablets bid with meals for 48 weeks (treatment arms A and B1) or for 60 weeks (treatment arm B2)

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
All-trans retinoic acid (Tretinoin) (VESANOID®), pegylated interferon alpha-2a (PEGASYS®), ribavirin (COPEGUS®)

Primary outcome(s)
To compare the parameter Md (corresponding to an increase in the elimination rate of infected hepatocytes during treatment) of HCV viral kinetics for therapy with the combination of pegylated interferon alpha-2a, ribavirin and all-trans retinoic acid versus the combination of pegylated interferon alpha-2a and ribavirin. Based on viral load measurements at BL, days 1, 2, 3, weeks 1, 2, 3, 4, 6, 8 and 12 (treatment groups A and B) by means of the Roche COBAS Ampliprep™/COBAS TaqMan™ Test (lower limit of detection less than 12 IU/ ml) Md will be determined for each individual patient.

Key secondary outcome(s)
1. Analysis of frequence and function of CD4+ and CD8+ T-cells, of dendritic cells, of NK-cells as well as of CD4+/CD25+ regulatory T-cells and additionally of interferon-induced plasma chemokines (CXCL9, CXCL10, CXCL11, CXCR3) for comparison of treatment groups A and B at BL, weeks 1, 2, 4, 8 and 12
2. Comparison of parameter e (corresponding to the antiviral efficiency) of HCV viral kinetics between treatment groups A and B on the basis of kinetic equations fitted for each individual patient
3. Comparison of early virological response rates (EVR, defined as at least a 2 log drop of HCV-RNA at treatment-week 12) between the combination of standard dose Peginterferon alfa-2a and Ribavirin (treatment group B), versus the same therapy combined with All-trans Retinoic acid (treatment group A)
4. Comparison of Sustained Virological Response rates (SVR) (defined as non-detectable HCV-RNA 24 weeks after the end of therapy), End Of Treatment virological response rates (EOT) (defined as non-detectable HCV-RNA at the end of therapy with at least 40 weeks of therapy) and week-24 virological response rates measured by Roche COBAS Ampliprep™/COBAS TaqMan™ Test (lower limit of detection less than 12 IU/ ml) between the combination of pegylated interferon alpha-2a, ribavirin and all-trans retinoic acid (treatment group A) and the combination of pegylated interferon alpha-2a and ribavirin (treatment group B1) (for this evaluation patients with a decrease in HCV-RNA of less than two log at week 12 will be classified as non-responders. This refers to all patients in group B2 and some patients in group A)
5. Comparison of the different virological response rates and the immunological responses between treatment groups A (combination with All-trans Retinoic acid from week 0 to week 12)

and B2 (combination with All-trans Retinoic acid from week 12 to week 24)
6. Evaluation of safety and tolerability of combination therapy with pegylated interferon alpha-2a, ribavirin and all-trans retinoic acid

Completion date
31/10/2010

Eligibility

Key inclusion criteria
1. Serological evidence of chronic Hepatitis C infection by positive anti-HCV testing and detectable HCV-Ribonucleic Acid (RNA) in serum (greater than 100 IE/ml)
2. Non-responder to the previous anti-HCV combination therapy with pegylated interferon and ribavirin. Non-response is defined as a lack of at least a greater than two log drop in HCV-RNA at any time point during the previous therapy of at least 12 weeks, or a greater than two log drop at week 12, but HCV-RNA still detectable at week 24. During the previous course pegylated interferon and ribavirin had to be administered in standard dose, that is, for example, at least 1.0 µg/kg/body weight/week pegylated interferon alpha-2b and 800 mg/d ribavirin at the beginning or at least 135 µg/week peginterferon alpha-2a and 800 mg/d ribavirin at the beginning
3. Evidence of HCV genotype 1 by means of reverse hybridisation assay Inno LiPA from Bayer Versant (Innogenetics) within 24 months before randomisation
4. Histological evidence of inflammation and fibrosis (greater than F1) in the liver with or without evidence of compensated cirrhosis within 24 months before randomisation (Child-Pugh grade A)
5. The previous anti-HCV therapy course had to be finished at least 6 months before randomisation into this study
6. Men and women aged 18 to 65 years
7. Negative urine- or serum-pregnancy test for women with childbearing potential within 24 hours before administration of the first dose of medication (also for fertile female partners of male patients)
8. For female patients: during administration of the study medication and during 6 months of treatment free follow-up two highly effective methods of contraception have to be used, one of them with a barrier function, that is condom (accepted methods of contraception are: combined oral contraceptives, implants, injectables, some Intra-Uterine Devices [IUDs], vasectomised partner) (note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals, CPMP/ICH/286/95 mod); micro-dosed gestagenes ("Minipill") and oral contraceptives with a content of less than 20 µg ethinylestradiol as a method of contraception are not sufficient when all-trans retinoic acid is used
9. For male patients and their female partners: during administration of the study medication and during 7 months of treatment free follow-up two highly effective methods of contraception have to be used, one of them with a barrier function, that is condom (accepted methods of contraception are: combined oral contraceptives, implants, injectables, some IUDs, vasectomised partner) (note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals, CPMP/ICH/286/95 mod); micro-dosed gestagenes ("Minipill") and oral contraceptives with a content of less than 20 µg Ethinylestradiol as a method of contraception are not sufficient when all-trans retinoic acid is used
10. Written informed consent concerning the participation in the study
11. An ophtalmological examination is recommended for all patients before randomisation

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
57

Key exclusion criteria
1. Known hypersensitivity to the active substance of pegylated interferon alpha-2a, to alpha-interferons or ribavirin or one of the other ingredients
2. Known allergy to a substance of the class of retinoids or one of the other ingredients (e.g. allergy to soy beans or peanuts)
3. Persons under age or persons of age, that are not able to realise nature, meaning and significance of the clinical study and to adjust their will in that sense (according to section [§] 40 Abs. 4 and § 41 Abs. 2 and Abs. 3 AMG [Arzneimittelgesetz] - the German law which regulates clinical trials)
4. Pregnancy or breastfeeding
5. Fertile women, not using highly effective methods of contraception
6. Male partners of pregnant women
7. Participation in another clinical study at the same time or within the last three months
8. Patients already included once into this study
9. Persons, that are eventually in dependence on the sponsor or investigator
10. Infection with HCV-Genotypes-2, -3, -4, -5 or -6
11. Evidence of Hepatitis B surface Antigen (HBsAg), Human Immunodeficiency Virus (HIV)-antibodies during screening
12. Patients under immunosuppression
13. Treatment with systemic anti-neoplastic or immune modulatory medication (including supraphysiological doses of steroids or radiation) within the last 6 months before randomisation and throughout the whole study duration
14. Chronic hepatitis unrelated to Hepatitis-C-virus (e.g. haemochromatosis, autoimmunehepatitis, metabolic- or alcohol-related liver disease)
15. Decompensated cirrhosis or liver disease graded Child-Pugh grade B or C
16. Signs of a Hepatocellular Carcinoma (HCC) before randomisation in case of a state of cirrhosis or transition to cirrhosis (alpha-fetoprotein values greater than 100 ng/ml lead to exclusion of the patient from the study, with values of alpha-fetoproteins of greater than 50 ng /ml and less than 100 ng/ml an HCC should be excluded by means of an established method)
17. Oesophagael varices with bleeding in the medical history
18. Haemoglobin less than 12 g/dl for women and less than 13 g/dl for men during screening
19. Patients with an elevated risk for anaemia (e.g. thalassemia, spherocytosis, etc.) or patients,

for whom anaemia would be a medical risk in particular
20. Neutropenia less than 1,500/µl or thrombocytopenia less than 70,000/µl during screening
21. Creatinine in serum greater than 1.5 mg/dl during screening
22. Acute or known psychic illnesses or disturbances that negatively influence the ability of the patient to understand the requirements of this study
23. Severe depression in the medical history, defined as any sign on suicidal tendencies, or hospitalisation because of depression, or any exclusively antidepressive therapy of at least 3 months duration (an accompanying antidepressive treatment in the setting of a previous anti-HCV therapy with Interferons is allowed)
24. Severe psychotic or any other severe psychiatric disease in the medical history, defined as any antipsychotic or otherwise psychiatric treatment of at least 3 months duration in the medical history or any sign on suicidal tendencies or hospitalisation because of these illnesses
25. Patients with the state of excitation or irritation
26. Patients with deliriant syndromes as well as exogenous psychosis in their medical history
27. Epilepsia
28. Autoimmune diseases (e.g. chronic inflammatory bowel disease, idiopathic thrombocytopenic purpura, lupus erythematosus, sclerodermia, severe psoriasis, rheumatoid arthritis)
29. Disturbances in thyroid function, impossible to adjust euthyroid by medication
30. Insufficiently adjusted diabetes mellitus (HbA1c greater than 7%) or insufficiently adjusted hypertriglyceridaemia (greater than 350 mg/dl)
31. Clinically manifest gout
32. Chronic pulmonary disease with functional restriction
33. Severe cardiac disease (e.g. cardiac insufficiency New York Heart Association [NYHA] class III or IV, myocardial infarction within the last 6 months, ventricular Tachy¬arrhythmia in need of treatment, instable angina pectoris, cerebrovascular circulation disturbance or any other significant cardiovascular disease)
34. Organ transplantation except cornea transplantation
35. Cancer within the last 5 years (with the exception of an adequately treated basaliom) or any other serious disease, that, in the investigators perspective, represents an exclusion criterion for the study
36. Information on clinically relevant retina changes (e.g. in the case of Cytomegalovirus [CMV]-retinitis, macula degeneration or hypertensive or diabetic retinopathy)
37. Active drug abuse (including excessive alcohol consumption) within the last year before randomisation with the exception of a prescribed substitution medication
38. The following substances are not allowed in this study because of interacting potential with the study drugs or influence on the patients suitability for this study:
38.1. Vitamin A
38.2. Tetracycline
38.3. Antifibrinolytic agents such as tranexamic acid, aminocaproic acid, aprotinin, daunorubicin, cytarabin
39. Unwillingness or inability to give written consent after being informed
40. Any other clinical condition, that, in the investigators perspective, questions enrolment of that patient

Date of first enrolment
25/09/2007

Date of final enrolment
31/10/2010

Locations

Countries of recruitment
Germany

Study participating centre
University of Mainz
Mainz
Germany
55131

Sponsor information

Organisation
Johannes Gutenberg-University Mainz (Johannes Gutenberg-Universitat Mainz) (Germany)

ROR
https://ror.org/023b0x485

Funder(s)

Funder type
Industry

Funder Name
Johannes Gutenberg-University Mainz (Johannes Gutenberg-Universitat Mainz) (Germany)

Alternative Name(s)
Johannes Gutenberg University of Mainz, University of Mainz, Johannes Gutenberg University Mainz, JGU

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Germany

Funder Name
Roche Pharma AG (Germany) - supporting the trial

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		01/04/2013	10/06/2021	Yes	No