Study Identification

Unique Protocol ID: IFCI-04/10/2015

Brief Title: Autologous Dendritic Cell Vaccine for Treatment of Patients with Chronic HCV-Infection

Official Title: Safety/Efficacy of Vaccination with Autologous Dendritic Cells Pulsed with Recombinant HCV-Antigens (Core and NS3) for Treatment of Patients with Chronic HCV-Infection

The protocol was approved by the Ethics Committee of the Institute of Fundamental and Clinical Immunology (approval number: no 88, 04/10/2015)

Study Description

Purpose/Brief Summary:

Clearance of HCV infection requires earlyand multi-specific HLA class I restricted CD8+ T cell and class II restricted CD4+ T cell responses to both structural (Core) and non-structural HCV proteins (NS3, NS4A, NS5A, NS5B). Dendritic cells (DCs) are professional antigenpresenting cells that link innate and adaptive immune responses, and play a major role in priming, initiating, and sustaining strong anti-HCV T cell immune responses.

The general objective of this study is to evaluate safety, feasibility and clinical efficacy of therapeutic vaccinationin genotype 1 HCV patients using autologous DCs pulsed with recombinant HCV-antigens (Core and NS3). Expected effects: DC vaccination induces Core/NS3-specific immune response and reduces viral load in patients with chronic HCV-infection.

Condition	Intervention	Phase
Hepatitis C, Chronic	Biological: Autologous monocyte-derived dendritic cells,	Phase 1
	generated in the presence of IFN- α /GM-CSF and pulsed with recombinant HCV Core (1-120) and NS3 (1192-1457)	Phase 2
	proteins.	

Detailed Description:

Hepatitis C virus (HCV) has chronically infected an estimated 170 million people worldwide. People infected with HCV are at risk for developing chronic liver diseases, such as liver cirrhosis and primary hepatocellular carcinoma. It has been estimated that HCV accounts for 27% of cirrhosis and 25% of hepatocellular carcinoma worldwide. Therapy for chronically HCV-infected patients has involved a pegylated interferon-alpha and ribavirin (pegIFN/RBV) and is still the only FDA-approved therapeutic combination. However, this therapy is expensive, non-specific, toxic, and only effective in about 50% of genotype-1 HCV patients.

An early immune response, represented by the activation of NK cells, the development of vigorous anti-HCV CD4+ and CD8+ T-cell responses, and the appearance of HCV-specific antibodies, is mounted by the host during acute HCV infection and leads to clearance of the virus. However, in the vast majority (\approx 85%) of infected individuals HCV causes a persistent infection. The mechanisms of HCV persistence remain elusive and are largely related to inefficient clearance of the virus by the host immune system.

Although HCV genome is very variable with hundreds of serotypes and six genotypes, several structural (Core) and nonstructural proteins (NS3, NS4A, NS5A, NS5B) are highly conserved among genotypes and subtypes. It is apparent that clearance of hepatitis C infection requires early and multi-specific HLA class I restricted CD8+ T cell and class II restricted CD4+ T cell responses to both structural and non-structural HCV proteins.

DCs are professional antigen-presenting cells that link innate and adaptive immune responses. DCs play a major role in priming, initiating, and sustaining strong T cell responses against pathogen-derived antigens. Therefore DC-based therapy represents a promising immunotherapeutic approach in terms of their propensity to establish anti-HCV adaptive immune responses.

This trial is a prospective, non-blinded, interventional study to determine safety, feasibility and clinical efficacy of therapeutic vaccination in genotype 1 HCV patients using autologous DCs pulsed with recombinant HCV-antigens (Core and NS3). Our previous work has shown that the short-term loading of DCs with recombinant HCV proteins Core (1-120) and NS3 (1192-1457) have no any marked inhibitory effect on maturation and functions of DCs [Oleynik E.A., et al. 2016].

In experimental group thirty patients with chronic hepatitis C (genotype 1) will be vaccinated via intracutaneous injection of monocyte-derived DCs, generated in the presence of IFN- α /GM-CSF and pulsed with recombinant HCV Core (1-120) and NS3 (1192-1457) proteins. The vaccination protocol will includes initiating (one injection per week, no 4) and maintaining (one injection per month, no 6) courses with subsequent 6-month of follow up.

The safety will be determined by the evaluation of the number of participants with the adverse events. Liver safety will be assessed by blood analysis and Ultrasound. Patients will be monitored in a 2 months (after completing of initiating course), 7 months (after completing of maintaining course) and 13 months (in a 6 months post-vaccination follow-up).

Conditions

Conditions: Hepatitis C, Chronic; Liver Diseases; Hepatitis, Viral, Human; Hepatitis, Chronic; Virus Diseases.

Keywords: Dendritic Cells; DC-based Vaccines; Chronic HCV Infection; Antigen-Specific T cell response; Recombinant HCV-Core antigen; Recombinant HCV-NS3 antigen.

Study Design

Study Type: Interventional Primary Purpose: Treatment Study Phase: Phase 1/Phase 2 Intervention Model: Single Group Assignment Number of Arms: 1 Masking: No masking Enrollment: 30

Arms and Interventions

Arms	Assigned Interventions
Experimental: Autologous DC-vaccines	Biological/Vaccine: Autologous DC-vaccines
Thirty patients with chronic hepatitis C (genotype 1) will receive the initiating and maintaining courses of autologous monocyte-derived dendritic cells, generated in the presence of IFN- α /GM-CSF and pulsed with recombinant HCV Core (1-120) and NS3 (1192-1457) proteins.	Patients will be vaccinated via intracutaneous injection of autologous DCs (5×10^6) combined with adjuvant subcutaneous injection of recombinant hIL-2 (250 000 IU). Initiating course: one vaccination per week, during 1 month. Maintaining course: one vaccination per month, during 6 month. Patients will be monitored in a 2 months (after completing of initiating course), 7 months (after

completing of maintaining course) and 13 months (in a 6 months post-vaccination follow-up).

Outcome Measures

Primary Outcome Measure:

1. Number of Participants with Severe Adverse Reactions and/or With Abnormal Clinical Laboratory Values That Are Related to Treatment

[Time Frame: From enrollment and up to 13 months]

Frequency of severe adverse reactions will be evaluated from enrollment and up to 13 months. Liver safety by blood analysis (ALT, AST, GGT, Total and conjugated bilirubin, platelets, ESR, etc) and Ultrasound will be assessed from enrollment and up to 13 months (= baseline, 2, 7 and 13 months after 1-st vaccination).

Secondary Outcome Measure:

2. Number of Participants with Virological Response According to HCV RNA Viral Load [Time Frame: Baseline, 2, 7 and 13 month after 1-st vaccination]

Virological response in patients receiving DC-vaccinations is defined as change from baseline in HCV RNA viral load by at least 1 log at 2, 7 and 13 month after 1-st vaccination. Plasma level of HCV RNA will be measured by Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

3. Number of Participants Who Have Developed or Increased Anti-Viral Immune Response According to T-cell proliferation

[Time Frame: Baseline, 2, 7, and 13 months after 1-st vaccination]

Change from baseline in T-cell proliferative response to HCV Core and NS3 proteins at 2, 7 and 13 month after 1-st vaccination. T-cell proliferation will be evaluated using radiometry based on 3H-thymidine incorporation.

4. Number of Participants Who Have Developed or Increased Anti-Viral Immune Response According to $IFN-\gamma$ production

[Time Frame: Baseline, 2, 7, and 13 months after 1-st vaccination]

Change from baseline in T-cell IFN- γ -producing response to HCV Core and NS3 proteins at 2, 7 and 13 month after 1-st vaccination. Production of IFN- γ will be measured by ELISA kit

Eligibility

Minimum Age: 18 Years Maximum Age: 65 Years Sex: All Accepts Healthy Volunteers: No

Criteria:

Inclusion Criteria:

- Age 18 to 65 Years (Adult)
- Chronic hepatitis C (genotype 1b)
- HCV-positive patients
- Plasma HCV RNA level $\geq 10^4$ IU/ml
- Liver fibrosis (METAVIR Score 0-III)

- Patients must be able totolerate all study procedures
- Patients must be willing to voluntarily give written Informed Consent to participate in the study before any procedures are performed
- Patients must be willing to be available for all baseline, treatment and follow-up examinations required by protocol

Exclusion Criteria:

- Co-infection with hepatitis B, A, D, E, cytomegalovirus or Epstein-Barr virus
- Liver cirrhosis (METAVIR Score IV)
- The high degree of hepatitis activity (ALT and/or $AST \ge 10$ ULN)
- Received any vaccine within a month prior to study entry
- A history of diabetes
- Psychiatric disorders
- Renal dysfunctions
- Hemodynamic or respiratory instability
- HIV or uncontrolled bacterial, fungal, or viral infections
- Autoimmune diseases
- Pregnancy
- Malignancy
- Participation in other clinical trials

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References

Oleynik E.A., Leplina O.Y., Tyrinova T.V., Tikhonova M.A., Pyrinova G.B., Ostanin A.A., Starostina N.M., Chernykh E.R. The influence of recombinant HCV proteins Core and NS3 on maturation and functions of dendritic cells generated in vitro with interferon-alpha. Immunology 37 (5): 239-245, 2016. (in Russian) DOI: 10.18821/0206-4952-2016-37-5-239-245