HepCaRe

Hepatitis C antiviral Therapy Failure Registry

A joint study among the HEPVIR participants
HepCaR protocol
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Study participants
Participating HEPVIR members and other participating researchers.

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Background
Direct-acting antivirals (DAAs) for treatment of hepatitis C (HCV) have high cure rates of more than 90% \(^1\). Despite this excellent efficacy of DAAs, virological failure can occur often associated with resistance associated substitutes (RASs). RASs are rare but can be a limitation with high clinical impact leading to incurable cases.\(^2\) DAA resistance is driven by the selection of mutations at different positions in the NS3 protease, NS5B polymerase and the NS5A proteins. There are two different forms of RASs, first resistance can occur as a naturally occurring polymorphisms. Second, resistance associated mutations can emerge quickly in patients resulting in treatment failure, since HCV is a fast replicating virus. RASs remain present for weeks to many years after treatment failure, and have a huge impact on further treatment.\(^3,4\) This is because DAAs have a low genetic barrier (defined as the number of mutations required to overcome drug-selective pressure) to resistance with the exception of the NS5B nucleotide inhibitors. Therefore, resistance can have profound clinical implications as patients have to switch to different classes of DAAs and have to be treated for a longer period of time.\(^3\) Importantly, as a result of resistance, some patients have to be retreated with triple DAA therapy, ribavirin and are in some circumstances even incurable.\(^2,3\)

Most patients respond well to combinations of DAAs in randomized controlled trials\(^5\). DAAs only recently became available and their effectiveness in daily clinical practice can be lower than in the well-controlled randomized controlled trials. Since DAAs are only recently available, there is limited
real life data. In some cases failure in real life data is slightly higher due to compliance of the patients and a 80-90% DAA cure rate is achieved. The natural frequency of polymorphism differs between, HCV geno- and subtypes, geographic region and method of sequencing.

The risk of developing resistance associated substitutes during DAA treatment depends on host- and virus-related factors, the properties of the drugs used and the treatment strategies applied. In addition HCV genotype and stage of liver fibrosis have been established as independent parameters associated with virological failure. Real life data study is needed to identify patient characteristics or virological factors associated with resistance within all genotypes. Insight into the prevalence of the RASs in daily practice is, however, important as the emergence of resistance has an impact on clinical outcome. In addition, it is also important to gain insight into the mutational patterns that are found in patients failing treatment.

Objectives

- Analyze the mutational patterns that are associated with DAA resistance associated treatment failure
- Occurrence of resistance associated treatment failure in Europe

Definitions

Therapy failure:
- Non-response/viral relapse during DAA therapy
- Viral rebound within 1 year after completion of therapy (excluding re-infection with HCV sequence analysis)

Study design

Observational European multi-center study

Inclusion criteria

- Men or women > 18 years old
- PCR confirmed HCV infection
- Established therapy failure on DAA regimen
- Available sequence or sample for sequencing

We strongly encourage a baseline sequence

Study population
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The population contains men/woman > 18 years old who have failed on DAA therapy for across multiple clinical sites. Datasets contain patients characteristics, clinical data, viral load measurements and viral genotyping results.

Data collection

Data are going to be collected using an online form available at http://hepvir.crp-sante.lu/, data can be submitted on a per-patient basis. Data will be stored on a server at Luxembourg institute of Health (Strassen, Luxembourg). Submitted datasets can only be accessed by the principal investigators. In addition, individual submitters can access and review their submitted data at any time prior to analysis. Access-codes will be distributed on demand by the assistant executive officer of the ESAR.

See supplement 1 for full dataset information.

Longitudinal data

If multiple resistance analyses have been performed on different samples of an individual patient, these should be considered as separate entries. Thus each with concurrent serological and clinical data coupled to the genotypic analysis draw date.

Drug resistance

Assessment of the impact of drug resistance on therapy response will be performed by using web-based resistance interpretation algorithms.

Data analysis and reports

Analysis of collected data will be performed after a sample size of n=500 has been reached. Data collection progress and interim results will be reported at meetings of the ESAR.

Ethical approval

This registry will only include data that are already available. Patients will not be approached to obtain additional samples or information. Every submitter is responsible for obtaining ethical approval if needed according to national guidelines. For our Dutch participants a copy of METC approval can be requested by our study coordinator.

Confidentiality of records

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Partners are responsible for assuring anonymity of their patients. Patients should not be identified by name or submitted data, or during verbal communications. Patients are allocated a study number, with which only the submitter can identify the patient. In addition only the year of birth, and not the date, will be recorded.

Governance

The ESAR-HEPVIR database will contain all data submitted for HepCare. Submission of data to the HepCaRe database does not affect original ownership of data. The owner of the data reserves the time right to review or withdraw submitted data at any time prior to submission of the final manuscript. Permission of the submitters will be requested for any new analysis which is not described in the objectives of this protocol. No transfer of a centre’s data will be performed without a written consent of the submitter. Primary analysis will be the patterns of resistance in relation to the genotype and drug regimens used. Secondary analysis may be done in the future but permission needs to be obtained from all principal investigators.

Publication of data

Data of the study will be published, but will not include any representations of patients that compromise their confidentiality. All submitters will be asked for comments on the manuscript before it is submitted to a journal as a joint publication.

Guidelines for authorship

Per research group a maximum of two researchers/clinicians, in addition to researchers actively involved in the analysis, may be included in the list of authors. Other participants can be included in the Study Committee list.

Supplement:

1) Dataset information
2) References
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## Dataset information
- Unique patient identification number*
- Submission country*
- Center*
- Abstractor Initials*

## Demographics
- Year of birth*
- Gender*
- Country of birth
- Region of residence

## Clinical data – HCV status
- Possible route of infection*
- Fibrosis stage(+date)*
- Fibrosis staging tool

## Clinical data – HCV past therapy
- Type of previous therapy*
- Start/stop dates previous therapy*
- Outcome*
- Peg-intron/Peg-assays
- Ribavirin dosage
- Dose change
- Viral rebound at week no*
- Latest prior NS3 sequence
- Latest prior NSSA sequence **

## Clinical data – Current HCV therapy
- Current HCV therapy*
- Start/stop dates therapy*
- Peg-intron/Peg-assays
- Ribavirin dosage
- HCV genotype*
- Outcome*
- Viral rebound at week no*
- HCV RNA assay
- Co-medication
- Room for comments co-medication
- Clinical reasons for therapy failure

## Clinical data – Viral load measurements
- Baseline viral load*
- Draw date*
- Viral load under therapy*
- Draw dates*

## Clinical data – Viral resistance data
- Sequence*
- Draw date*
- Sequence method
- Type of sample for sequence
- Laboratory performing sequencing

## Clinical data – Co-infection status
- HBV/HIV co-infected*
- HIV baseline viral-load
- HBV baseline viral-load
- Current HBV/HIV therapy

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CD4 at time of start current HCV therapy
CD4 at time of therapy failure current HCV therapy

(* are required data fields, data can be submitted if these field are completed. ** will be added to the database.)

4. Susser S. Long-Term follow-up analysis of RAVs in HCV NS3, NSSA, and NSSB in DAA therapy failure patients EASL 2015.