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Letter to the Editor

Four weeks of ledipasvir/sofosbuvir and ribavirin with or without pegylated interferon for chronic hepatitis C in non-cirrhotic people who inject drugs. A randomized trial

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Title
Four weeks of ledipasvir/sofosbuvir and ribavirin with or without pegylated interferon for chronic hepatitis C in non-cirrhotic people who inject drugs. A randomized trial

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Running title: The 4 WIDUC study

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Clinical trials register: Eudract nr: 2014-005589-31, the 4WIDUC trial

Contributions to the paper. Anne Øvrehus and Peer Christensen designed the trial with the assistance and intellectual contribution from Inge Birkemose. Anne Øvrehus performed the data analyzes with assistance from Peer Christensen. Henrik Krarup and Anja Ernst made significant contributions in the analysis of viral resistance data and contributed to the manuscript. Dorte Holm and Belinda Mössner contributed to the writing of the manuscript and the acquisition of data.

Conflicts of interest None of the authors have any conflicts of interest in the present study. Anne Øvrehus have for other studies received grants from Gilead Sciences Nordic Fellowship and personal fees or travel support from Gilead, MSD, Abbvie, and BMS. Peer Christensen has received research grants from Abbvie, MSD, BMS, Gilead Sciences and Roche. Belinda Mössner Dorte K. Holm, Anja Ernst, Inge Birkemose and Henrik Krarup reports no conflict of interest

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To the editor

The success of direct acting anti virals (DAA) in curing chronic hepatitis C (CHC) infection is well documented and most patients can achieve sustained virological response at week 12 (SVR12) with 8-12 weeks of therapy (1). However as DAA therapy is accessed by populations of challenged life circumstances, such as people who inject drugs (PWID), adhering to treatment for several months might be more difficult. This issue was evident in multiple presentations at the recent International Network for Hepatitis in Substance Users 2017 meeting (2).

We would therefore, in the context of treating hepatitis C for elimination as a public health threat as defined by the WHO (3) like to draw your attention to a pilot trial of 4 weeks treatment for CHC that we conducted in 2015-2016. ( Eudract nr: 2014-005589-31, the 4WIDUC trial, presented at ILC 2017 as oral e-poster THU-225). The original aim of the trial was to investigate if adding interferon to DAAs+ribavirin (RBV) could reduce treatment duration to 4 weeks across genotypes and maintain acceptable SVR 12 rates in CHC patients with favorable baseline characteristics for cure in a target population of PWID.

At the time of trial design there were no published results on 4 week trials and models of HCV viral kinetics predicted that 4 weeks of viral suppression might be too short to achieve cure (4).

However case reports including cases from clinical trials on DAA with premature treatment abruption have documented cure with 4 weeks of treatment or less. The very high SVR 12 rates with 8-12 weeks of therapy also indicates that a subset of “easy to treat” patient might be cured with shorter treatment. We therefore designed inclusion criteria to exclude patients with negative predictors for treatment success such as high viral load (VL), obesity, older age, significant liver fibrosis/cirrhosis and being treatment experienced (5, 6).
As DAA-backbone ledipasvir/sofosbuvir (LDV/SOF) was chosen as the most potent combination available in 2014 across genotypes. After initiation of the trial LDV/SOF+RBV was reported to be less efficient in genotype 3 patients with severe liver disease but as results in mild diseases were still acceptable the trial continued unchanged(7). High dose RBV at 15 mg/kg were in some trials(interferon era) more favorable than fixed dose and used in the trial. Pegylated interferon 2a(INF) was chosen as the interferon option.

The study was conducted at an outreach drug treatment center targeting mainly the PWID population because this in our setting would be the main real life target populations for short treatment.

We randomized persons 1:1 to receive 4 weeks of LDV/SOF 90/400 mg qd. and RBV qd.(15mg/kg max. 1400 mg) with/without the addition of 180 µg INF once weekly.

Main inclusion criteria: Having CHC of all genotypes (defined as two consecutive HCV-RNA positive blood samples within 2 years), 18-49 years of age, HCV-RNA VL≤ 2.000.000 IU/ml, treatment naïve, weight<100 kg or BMI<30 kg/m^2, liver stiffness measurement(LSM)<8 kPa and no signs of liver cirrhosis.

None of the study subjects were eligible for standard of care treatment due to fibrosis (F2 or LSM>10kPa) treatment restrictions in Denmark(still valid).

The study was approved by the Danish Health and Medicines Authorities, The Regional Committees on Health Research Ethics for Southern Denmark and monitored by the Good Clinical Practice institute at the University of Southern Denmark in compliance with the Good Clinical Practice Guidelines and the Declaration of Helsinki.
The study planned to enroll 40 persons over 52 weeks and was powered to detect a 20% difference between treatment arms with an assumed 80% cure rate with interferon and 50% without.

The study was conducted in April 2015-April 2016 at a single center; the hepatitis clinic at the municipal drug treatment center in Odense, Denmark. The clinic is an outreach branch of the Department of Infectious Diseases at Odense University Hospital. It is a service for drug users in treatment not wanting or not able to attend hospital based care. Patients were offered participation in the study either at their routine visits at the hepatitis clinic or invited for information by the clinic staff.

Study treatment was aligned with patients’ drug use treatment (daily observed or take homes). Study treatment could continue outside the drug treatment center if necessary. Patients had scheduled study visit including blood tests for safety and VL at treatment week (TW) 0, 1, 2, 3 and 4 and at post-TW 4, 12 and 24. Blood for viral whole genome sequencing (WGS) was collected at screening and at post-TW 4, 12 and 24. WGS for resistance associated substitutions (RAS) were performed in treatment failures only, using Ion Proton (Life Technologies, Carlsbad, CA, USA) and the Geno2pheno platform.

As of April 2015 there were 115 persons aged 18-49 years registered at the clinic. Of these 58% were not screened mainly due to known cirrhosis or lost to follow-up. A total of 48 persons gave informed consent, 12 failed screening, 5 of these due to high viral load and the remaining due to lost to follow-up or worsening of preexisting psychiatric co-morbidity. In total 36 patients were randomized (18 in each arm) and 32 initiated therapy (16 in each arm) and constituted the
intention to treat (ITT) population (please refer to CONSORT flow diagram in supp.). The baseline characteristics (ITT) is presented in table 1.

The trial stopped at the planned end date with 36 randomized subjects. Further inclusion was considered futile given the (high) cure rates observed in both arms making conclusions on the primary aim unlikely.

The per protocol population (PP) excluded those with no SVR 12/24 visit making the PP population 15/13 in INF+/INF-. No patients with missing SVR 12/24 visit had completed treatment.

In the ITT population SVR 12 was 92% and 75% for subjects in the INF+/INF- arm respectively and in the PP population 100% vs. 92% (figure 1).

The one treatment failure in the PP population was a male patient in the INF- arm. He completed treatment, had undetectable VL at TW 3, genotype 2a/2b virus with a L31M RAS in the NS5A domain at baseline and at viral recurrence (post-TW 4).

Viral kinetics during treatment showed no difference between groups looking at percentage of participants having undetectable (<10 IU/ml) or unquantifiable (<15IU/ml) VL at TW 1, 2, 3 or 4.

Having missed more than 10% of DAA doses occurred in 1 vs. 4 in INF+/INF- patients. Two patients completed treatment and parts of follow-up outside the drug treatment center due to hospitalization/incarceration (not related to therapy).

Treatment was in general well tolerated with few severe adverse events (5 events in 3 persons in each group). One was treatment related (asymptomatic neutropenia in the INF+ arm). The most prevalent adverse events were flu like symptoms (81%) in the INF+ arm and nausea in the INF- arm (50%). Median drop in hemoglobin from TW 0 to 4 was 1.0(-2.5--0 .3) and 0.95(-2.1 +0.5) mmol/l
in INF+/INF- respectively (p=0.76). RBV was dosed qd. in all but one person, no RBV dose reductions were done, but on person stopped RBV day 25 due to gastrointestinal side effects. Three persons (19%) had premature termination of interferon. One person received an initial dose of 90 µg and stopped due to subjective intolerance (completed on LDV/SOF+RBV alone) and two persons were withdrawn from INF TW 4 dose due to safety (neutropenia and failure to comply with study protocol blood tests respectively).

The study presented here is small but we think it raises a number of questions for future consideration. Shortening therapy to only 4 weeks for selected genotype 1 and 3 patients gave high SVR 12 rates. Small sample size and unintended skewness in genotypes between treatment arms makes conclusions as to the value of adding INF difficult especially in the context of LDV/SOF having proved to be inferior in genotype 3. Side effects, safety and monitoring makes INF an unappealing option given the treatment options we have today.

The value of RBV cannot be assessed in this trial as all persons received the drug but RBV has in hard to treat patients shown the ability to shorten treatment duration and improve cure rates. The long half-life of RBV and its ability to reduce viral replicative fitness by introducing frameshift mutations might be important in the post treatment phase. The use of RBV is what separates this study from three trials on 4 different DAA combinations given for 4 weeks published in 2015-2016. They reported SVR 12 rates from 20-40%. Besides using DAA-only without RBV or INF, trial populations were older (mean or median age 52-58 years) and included patients with higher viral loads and slightly more advanced fibrosis (8-10). These trials also reported that treatment failures were retreated with 12 week regimens with success and with no treatment emergent RAS (9, 10). Generating treatment emergent resistant associated substitutions (RAS) with short course DAA
treatment is an intuitive concern, neither this study nor the studies mentioned above have found RAS to be a problem in short course treatment.

The study also indicates that adherence to therapy and follow-up will be an issue and having effective ultra-short treatment options might be valuable even if this means including RBV when we expand treatment to population with ongoing transmission. Even though 4 weeks treatment should only be further investigated in patients with favorable baseline characteristics this is the majority of patients we need to treat in our setting in forthcoming years.

In conclusion we believe this study raises the question if adding RBV to a potent pan genotypic DAA is an option worth exploring further if aiming at shortening therapy to 4 weeks. Better designed and larger studies are surely needed. Future trials might also elucidate the relative importance of RBV(dose), age, liver fibrosis and viral load for an successful outcome in ultra-short treatment.
References

SVR 12 rate for the ITT and PP population

In the intention to treat analysis, 94% in the interferon arm and 75% in the interferon-free arm (p=0.14) achieved SVR12. One patient in the interferon arm and 3 patients in the interferon free arm dropped out/lost to follow up making SVR12 in the per protocol population 100% and 92% respectively (p=0.28).
Table 1
Baseline characteristics of the intention to treat cohort

<table>
<thead>
<tr>
<th>Baseline values and demographics</th>
<th>Arm 1 INF+ LDV/SOF/RBV+PEG 2a n= 16</th>
<th>Arm 2 INF- LDV/SOF/RBV n= 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Median(range)</td>
<td>39.6 (26.4- 48.2)</td>
<td>39.2 (29.2- 46.1)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 14 Female 2</td>
<td>Male 11 Female 5</td>
</tr>
<tr>
<td>Genotype</td>
<td>1a 2 1b 2 2 3</td>
<td>1a 2 1b 2 1 3</td>
</tr>
<tr>
<td>Weight in kilograms, Median(range)</td>
<td>73 (56-91)</td>
<td>76 (45-99)</td>
</tr>
<tr>
<td>BMI kg/m², Median(range)</td>
<td>23.8 (17.1- 29.0)</td>
<td>25.0 (17.1- 31.4)</td>
</tr>
<tr>
<td>IL28b subtype</td>
<td>CC 3 CT/TT 13</td>
<td>6 10</td>
</tr>
<tr>
<td>Viral load (x10³ IU/ml) at screen, Median(range)</td>
<td>169.5 (7.54-1140)</td>
<td>149.5 (7.05-1730)</td>
</tr>
<tr>
<td>Fibroscan in kPa, Median(range)</td>
<td>5.3 (3.5-7.9)</td>
<td>5.1 (3.6-7.9)</td>
</tr>
<tr>
<td>Baseline blood tests</td>
<td>Hemoglobin mmol/L 9.5 (7.1-10.7)</td>
<td>8.9 (6.4-9.8)</td>
</tr>
<tr>
<td></td>
<td>Neutrophils x 10⁹/L 4.4 (2.2- 12.2)</td>
<td>5.6 (1.8-11.2)</td>
</tr>
<tr>
<td></td>
<td>Platelets x 10⁹/L 237 (152- 332)</td>
<td>256 (167-364)</td>
</tr>
<tr>
<td></td>
<td>ALT IU/L 68 (26-205)</td>
<td>50 (31-183)</td>
</tr>
<tr>
<td></td>
<td>Bilirubin umol/L 8.5 (5-22)</td>
<td>6.5 (3-18)</td>
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<tr>
<td></td>
<td>Albumin g/L 43 (39-49)</td>
<td>42.0 (39-46)</td>
</tr>
<tr>
<td>Alcohol overuse past year</td>
<td>Yes 7 No 9</td>
<td>Yes 3 No 13</td>
</tr>
<tr>
<td>Years since start injecting,</td>
<td>16.0 (2-27)</td>
<td>13.5 (2-30)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active injecting yes/no</td>
<td>Yes 6 No 10</td>
<td>Yes 5 No 11</td>
</tr>
<tr>
<td>Opium substitution treatment</td>
<td>Heroin (legal)* 8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Methadone 5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine 3</td>
<td>3</td>
</tr>
<tr>
<td>Treatment delivery</td>
<td>Daily observed</td>
<td>9</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Take home weekly</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ribavirin dose plan</th>
<th>RBV mg/day, Median(range)</th>
<th>1000 (800-1400)</th>
<th>1200 (600-1400)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mg/kg/day, Median(range)</td>
<td>14.2 (12.7-15.6)</td>
<td>14.9 (13.3-17.4)</td>
</tr>
</tbody>
</table>

*p=0.05 when comparing genotype 1 vs. 3 between treatment arms using Pearsons chi2.

Legal heroin is an option for the most severely affected drug users as a harm reduction measure where methadone and buprenorphine has failed to stabilize the patient sufficiently. Legal heroine involves supervised injection once or twice daily.