Treatment of chronic hepatitis C genotype 1, 2 and 4 in patients with or without HIV and living in Central or West Africa: the TAC ANRS 12311 trial.

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Conflicts of interest

- Expertise boards, travel grants and study grants: Gilead Sciences, Janssen, Merck Sharp and Dome, Abbvie

- Gilead Sciences gave the drugs for the trial but did not participate in the analysis or interpretation of the data

- ANRS sponsored the trial
Background

Change in the paradigm of HCV treatment thanks to the efficacy and tolerability of DAAs

WHO commitment to reach 90% of those infected to be diagnosed, 80% of those diagnosed to be started on treatment, 90% of those on treatment to be cured, for a 65% decrease in liver-associated mortality by 2030

Reaching global HCV elimination is a realistic goal

Reality in Sub-Saharan Africa:
- High health burden associated to chronic hepatitis including HCV
- Almost no National Hepatitis Plan
- No universal screening policies and usual tools non adapted to resource-limited settings
- No access to DAAs in most countries and in those where treatment is available, only the private sector provides treatment

1 Hill, Science 2014
3 Lemoine, J hepatol 2015.
The TAC research project

ANRS 12311
CLINICAL TRIAL

ANRS 12336
DIAGNOSTIC STRATEGIES

1

ANRS 12342
SOCIO-BEHAVIORAL
STUDY

ANRS 12376
MORBIDITIES
(HBsAg reactivation)

COST-EFFICACY
ANRS 12342

AS 2017
Objectives of the trial

**Main objective:** Evaluate the efficacy (sustained virological response 12 weeks after end of treatment) of a 12-week course of an interferon-free regimen containing sofosbuvir and weight-based ribavirin (genotype 2), sofosbuvir and ledipasvir (genotype 1 and 4) in treatment naïve patients infected with HCV genotype 1, 2 or 4 in West and Central Africa (Senegal, Cameroon, Côte d’Ivoire).

**Secondary objectives:**
- Clinical and biochemical tolerability and safety
- On treatment - HCV kinetics and analyse its determinants
- Sustained virological response 24 weeks after end of treatment (SVR24)
- Provide capacity building in virology and use of elastometry
- **Build a network of clinicians, biologists, patients associations, and stakeholders in order to improve knowledge in the field of hepatitis C and grant larger access to HCV drugs**
Main eligibility criteria

**Inclusion criteria**
- Confirmed G1, G2 or G4 HCV infection
- Plasma HCV-RNA >12 IU/ml or the detection limit of the participating site
- No history of HCV treatment of any kind
- On birth control method
- In case of HIV infection:
  - Confirmed HIV-1 infection
  - Stable HIV treatment for at least 8 weeks
  - Current CD4+ lymphocytes count ≥100/mm³
  - Current plasma HIV-1 RNA <200 copies/mL

**Non inclusion criteria**
- Coinfection with HBV (HBsAg+)
- Cirrhosis child Pugh B or C
- In case of HIV infection:
  - Recent severe OI (<6 months)
  - Bad expected adherence
**Study design**

- **Primary endpoint:**

- **Secondary endpoints**
  - HIV, HCV kinetics, tolerability

- **Treatment groups:**
  - Sofosbuvir-Ledipasvir 400mg/90mg
  - Sofosbuvir 400 mg /day
  - Ribavirin 1000 or 1200 mg

- **Patient numbers:**
  - N=40
  - N=80

**Data analysis**

- **Fleming/A Hern’s design:**
  - Target efficacy level=70%
  - Inacceptable efficacy level=50%
  - Alpha=5%
  - Beta=20%

- **Study details:**
  - 40 patients in each group of genotype
  - Binomial 95%CI are built for this presentation
  - Preliminary results on 110/120 patients up to W24
  - Study ongoing – LPLV in November 2017
## Baseline characteristics (1/2)

<table>
<thead>
<tr>
<th></th>
<th>Genotype</th>
<th>Genotype</th>
<th>Genotype</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 n=33</td>
<td>2 n=40</td>
<td>4 n=37</td>
<td>n=110</td>
</tr>
<tr>
<td>Male, n (%):</td>
<td>17 (52)</td>
<td>25 (63)</td>
<td>19 (51)</td>
<td>61 (55)</td>
</tr>
<tr>
<td>Age (year), median (IQR)</td>
<td>59 (51 - 63)</td>
<td>52 (41 - 60)</td>
<td>61 (56 - 63)</td>
<td>58 (48 - 63)</td>
</tr>
<tr>
<td>BMI (Kg/m2), median (IQR)</td>
<td>23.4 (19.9 - 25.8)</td>
<td>24.3 (21.9 - 27.6)</td>
<td>27.9 (24.2 - 31.2)</td>
<td>25.0 (22.0 - 28.1)</td>
</tr>
<tr>
<td>Alcohol, Yes, &lt;once a day, n (%):</td>
<td>2 (6)</td>
<td>9 (23)</td>
<td>11 (30)</td>
<td>22 (20)</td>
</tr>
<tr>
<td>HIV infection, n (%):</td>
<td>6 (18)</td>
<td>12 (30)</td>
<td>14 (38)</td>
<td>32 (29)</td>
</tr>
<tr>
<td>Cirrhosis (APRI low &gt;1), n (%):</td>
<td>4 (12)</td>
<td>10 (25)</td>
<td>9 (24)</td>
<td>23 (21)</td>
</tr>
<tr>
<td>(APRI high &gt;2), n (%):</td>
<td>0</td>
<td>6 (15)</td>
<td>5 (14)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>logHCV-RNA (IU/mL), median (IQR):</td>
<td>5.8 (5.2 - 6.2)</td>
<td>6.0 (5.3 - 6.4)</td>
<td>6.3 (5.8 - 6.7)</td>
<td>6.0 (5.5 - 6.5)</td>
</tr>
<tr>
<td>ALT (IU/L) at W0, median (IQR):</td>
<td>50 (36 - 71)</td>
<td>46 (26 - 89)</td>
<td>49 (39 - 80)</td>
<td>47 (36 - 78)</td>
</tr>
<tr>
<td>ALT grade at W0:</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0</td>
<td>18 (55)</td>
<td>27 (68)</td>
<td>23 (62)</td>
<td>68 (62)</td>
</tr>
<tr>
<td>1.25 - 2.50 x ULN</td>
<td>14 (42)</td>
<td>7 (18)</td>
<td>9 (24)</td>
<td>30 (27)</td>
</tr>
<tr>
<td>&gt;2.50 - 5.00 x ULN</td>
<td>1 (3)</td>
<td>4 (10)</td>
<td>4 (11)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>&gt;5.00 - 10.00 x ULN</td>
<td>0</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Creatinin (mg/L), median (IQR):</td>
<td>8 (7 - 10)</td>
<td>9 (7 - 10)</td>
<td>8 (7 - 10)</td>
<td>8 (7 - 10)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), median (IQR):</td>
<td>13 (12 – 14)</td>
<td>14 (13 - 15)</td>
<td>14 (13 - 14)</td>
<td>14 (12 - 14)</td>
</tr>
</tbody>
</table>
## Baseline characteristics (2/2)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Genotype</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 n=6</td>
<td>2 n=12</td>
</tr>
<tr>
<td>WHO stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>2 (33)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>n (%)</td>
<td>3 (50)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>n (%)</td>
<td>1 (17)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>n (%)</td>
<td>0</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>CD4 (mm³)</td>
<td>median (IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>593 (454 - 625)</td>
<td>647 (391 - 738)</td>
</tr>
<tr>
<td>HIV viral load (cp/mL) &lt;50 cp/mL</td>
<td>n (%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>ABC-3TC-EFV</td>
<td>n (%)</td>
<td>0</td>
</tr>
<tr>
<td>ABC-3TC-LPV/r</td>
<td>n (%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>TDF-3TC-NEVIRAPINE</td>
<td>n (%)</td>
<td>0</td>
</tr>
<tr>
<td>TDF-3TC</td>
<td>n (%)</td>
<td>0</td>
</tr>
<tr>
<td>TDF-3TC-EFV</td>
<td>n (%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Time on ARV (months)</td>
<td>median (IQR)</td>
<td>23 (20 - 25)</td>
</tr>
</tbody>
</table>
Sustained virological response (SVR-12)

- SVR-12 by HCV genotype and overall:
  - Genotype 1: 87.3% (77.6 - 99.0)
  - Genotype 2: 90.0% (80.7 - 99.3)
  - Genotype 4: 89.2% (79.2 - 99.2)
  - Overall: 89.1% (83.3 - 94.2)

- SVR-12 by APRI score:
  - APRI score <=1: 90.0%
  - APRI score >1: 83.3%

- SVR-12 by HIV status:
  - HIV-: 90.0%
  - HIV+: 87.0%
Evolution of hemoglobin and ALT

- 4 patients with Hb decrease under 100g/L, 2 with subsequent RBV reduction
Tolerability and adherence

- No lost to follow-up
- Early discontinuation at W8 due to personal reason (travel abroad, but cured)
- 5 events occurred/aggravated between inclusion and W24 (validation of events ongoing)
- 2 new cases of arterial hypertension based on BP (2 measures with S>140 and D>90mmHg)

### Medication intake ratio at W12 (based on pill count)

<table>
<thead>
<tr>
<th></th>
<th>1 (n=27)</th>
<th>Genotype 2 (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sofosbuvir</td>
<td>-</td>
<td>94% (79% - 100%)</td>
</tr>
<tr>
<td>ribavirin</td>
<td>-</td>
<td>98% (92% - 100%)</td>
</tr>
<tr>
<td>sofosbuvir/ledispavir</td>
<td>100% (93% - 100%)</td>
<td>- 89% (71% - 100%)</td>
</tr>
</tbody>
</table>
Resistance genotyping in failing patients

HCV resistance genotyping in 4 failing patients:

<table>
<thead>
<tr>
<th>genotype</th>
<th>NS3/4</th>
<th>NS5A</th>
<th>NS5B</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>#2</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>#3</td>
<td>1</td>
<td>-</td>
<td>na</td>
</tr>
<tr>
<td>#4</td>
<td>1</td>
<td>-</td>
<td>L31M Y93H</td>
</tr>
</tbody>
</table>
Conclusion

Trial still ongoing, 2 patients awaiting SVR12 in August 2017

Interim SVR12 close to what is reported globally with the same DAs, with excellent tolerability and no safety issue

No impact of HIV on efficacy, safety, adherence

Suboptimal efficacy in cirrhotic naive patients

IT’S TIME TO SCALE UP HCV SCREENING AND ADVOCATE FOR TREATMENT ACCESS FOR THOSE IN NEED IN RESOURCE-LIMITED COUNTRIES TO MAKE GLOBAL HCV ELIMINATION A REALITY FOR ALL.
Acknowledgements

Centres médical de suivi des donneurs de sang (CMSDS, Treichville), Service d'Hépato-gastro-entérologie(CHU de Yopougon), SMIT de Fann / Centre régional de recherche et de formation de Fann (Dakar), Centre médical de la Cathédrale (Yaoundé), Hôpital de jour de l'Hôpital central (Yaoundé)


ANRS.