Utility of HCV antigen core quantification for the screening of chronic hepatitis C

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ATHS
2 octobre 2015
Continuum of biological follow-up in chronic hepatitis C
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- Challenge: change from a multi-step procedure to a two-step procedure
Techniques in development

• Point of care (POC) platform for HCV-RNA assays

  HCV RNA quantitative assay
    - Alere Q (*Alere Inc.*)
    - EOSCAPE-HCV rapid RNA assay (*Wave 80 Biosciences*)
    - Truelab Uno real time Micro PCR system (*Molbio Diagnostics Pvt Ltd*)
    - GeneXpert (*Cepheid*)
    - RT CPA HCV Viral Load Test (*Ustar Biotechnologies*)

  HCV RNA qualitative assays
    - Gendrive (*Epistem*)
    - PanNAT (*Micronics Inc.*)

Source: UNITAID report April 2015
Techniques in development

• HCV antigen core (AgC) quantification
  - To date, only one marketed test: Abbott ARCHITECT platform
  - One POC platform in development: DAKTARI
DAKTARI:
POC technology which eliminates sample preparation through the use of a technology known as “microfluidic immunochromatography”, which isolates cells (or viruses) :the only user step is to apply a drop of whole blood to the cartridge.
ANRS 12336 Study: Assessment of the performance of the HCV core antigen as a diagnostic tool for chronic hepatitis C in Africa

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Objective: to assess the efficacy of an antiviral treatment combining sofosbuvir and ribavirin for the treatment of genotype 1, 2 and 4 hepatitis C virus-infected patients in Sub-Saharan Africa

Therapeutic trial, phase IIb

N= 120 patients

Treatment: 3 to 6 months + 6 month-course of follow-up

Duration: October 2015- November 2016

Ancillary studies: medico-economic, diagnosis and screening
Objectives

**Principal objective:** Assessment of the performance of HCV core antigen quantification as a diagnostic tool for chronic hepatitis C in Africa

**Secondary objectives:**

- To assess the impact of the following covariables on the AgC diagnostic performance:
  - Demographic variables (age, gender)
  - HCV genotype
  - HIV infection
  - HBV infection
Methods

• AgC quantification: Abbott ARCHITECT HCV Ag Assay
  - < 3 fmol/L : negative
  - ≥ 10 fmol/L: positive
  - 3 ≤ [AgC] < 10 fmol/L: « grey zone » → retested twice

• HCV RNA quantification by quantitative rt-PCR : gold standard

• Anti-HCV Ab
• Anti-HHs Ab − ELISA serologies
• Ag HBs
Population

1037 serum samples from the Pasteur Center of Cameroon in Yaounde

**Inclusion criteria**
- HCV+:
  - HCV antibody (HCV Ab) positive serology
  - Quantifiable HCV RNA
- HCV-:
  - HCV Ab negative serology
  - OR undetectable HCV RNA
- HIV status known
- HBV status known

**Exclusion criteria**
- 11 Tri-infection (HCV/HIV/HBV)
- 7 Infection status unknown
- 10 Retest unavailable

**Included samples**: n=1009
- 475 VHC-
- 545 VHC+
Table 1: Socio-demographic and virologic characteristics of the sera

<table>
<thead>
<tr>
<th></th>
<th>Uninfected (n=335)</th>
<th>HCV-monoinfected (n=489)</th>
<th>HIV-infected (n=78)</th>
<th>HBV-infected (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV+ (n, %)</td>
<td>na</td>
<td>na</td>
<td>27 (34.6)</td>
<td>28 (59.6)</td>
</tr>
<tr>
<td>Gender, woman (n, %)</td>
<td>194 (57.9)</td>
<td>251 (51.3)</td>
<td>42 (53.9)</td>
<td>55 (51.40)</td>
</tr>
<tr>
<td>Age (mean, sd)</td>
<td>40.8 (17.5)</td>
<td>59.8 (11.2)</td>
<td>46.4 (13.7)</td>
<td>40.6 (15.1)</td>
</tr>
<tr>
<td>VHC+</td>
<td>na</td>
<td>na</td>
<td>57.3 (8.8)</td>
<td>54.9 (11.9)</td>
</tr>
<tr>
<td>VHC-</td>
<td>na</td>
<td>na</td>
<td>40.6 (12.2)</td>
<td>35.5 (12.7)</td>
</tr>
<tr>
<td>Genotype (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>na</td>
<td>45</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>na</td>
<td>39</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>na</td>
<td>37</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Virology (mean, sd)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARN VHC (IU/mL)</td>
<td>na</td>
<td>1 864 908 (2 339 039)</td>
<td>3 357 046 (4 613 890)</td>
<td>1 337 306 (1 676 788)</td>
</tr>
<tr>
<td>Indetectable HCV viral load</td>
<td>na</td>
<td>126</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>AgC VHC (fmol/L)</td>
<td>13.927 (251.28)</td>
<td>2063.24 (3073.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VHC+</td>
<td>na</td>
<td>na</td>
<td>4637.09 (7780.75)</td>
<td>1602.69 (2742.27)</td>
</tr>
<tr>
<td>VHC-</td>
<td>na</td>
<td>na</td>
<td>2.336 (6.820)</td>
<td>5.477 (41.17)</td>
</tr>
</tbody>
</table>
Results: correlation between AgC and HCV RNA, by infection group

**Figure 1a:** correlation between AgC quantification and HCV RNA in HCV mono-infected

Spearman $r=0.75$ ($p<0.00001$) $n=489$

**Figure 1b:** correlation between AgC quantification and HCV RNA in HIV-HCV co-infected sera

Spearman $r=0.84$ ($p<0.00001$) $n=27$

**Figure 1c:** correlation between AgC quantification and HCV RNA in HBV-HCV co-infected sera

Spearman $r=0.58$ ($p<0.001$) $n=28$
Results: AgC overall performance

Figure 2: ROC curves of the performance of AgC quantification for the diagnostic of chronic hepatitis C in HCV mono-infected and HCV uninfected, HIV-infected and HBV-infected patients.
Results: AgC’s overall performance

Table 2: Performance of the AgC quantification by infection group

<table>
<thead>
<tr>
<th>Infection Group</th>
<th>n</th>
<th>Se [IC97.5%]</th>
<th>Spe [IC97.5%]</th>
<th>VPP*</th>
<th>VPN*</th>
<th>AUC [IC95%]</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono</td>
<td>824</td>
<td>95.7 [93.2 ; 97.5]</td>
<td>99.7 [98.1 ; 100]</td>
<td>98.1</td>
<td>99.3</td>
<td>0.99 [0.98-1.0]</td>
<td>319</td>
<td>0.043</td>
</tr>
<tr>
<td>HIV</td>
<td>78</td>
<td>100 [85.0 ; 100]</td>
<td>88.2 [74.3 ; 96.2]</td>
<td>57.6</td>
<td>100</td>
<td>0.99 [0.97-1.0]</td>
<td>847</td>
<td>0</td>
</tr>
<tr>
<td>HBV</td>
<td>107</td>
<td>96.4 [79.2 ; 99.9]</td>
<td>96.2 [88.1 ; 99.4]</td>
<td>80.2</td>
<td>99.4</td>
<td>0.98 [0.95-1.0]</td>
<td>25</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Table 3: Performance of the AgC quantification by genotype among the mono-infected and not infected sera group

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>Se [IC 97.5%]</th>
<th>Spe [IC 97.5%]</th>
<th>VPP*</th>
<th>VPN*</th>
<th>AUC [IC95%]</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>488</td>
<td>97.7 [86.4-99.9]</td>
<td>98.9 [97.2-99.7]</td>
<td>93.4</td>
<td>99.6</td>
<td>0.99 [0.99-1.0]</td>
<td>88.8</td>
<td>0.023</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>482</td>
<td>94.9 [80.7-99.6]</td>
<td>98.9 [97.1-99.7]</td>
<td>93.2</td>
<td>99.2</td>
<td>0.99 [0.97-1.0]</td>
<td>86.3</td>
<td>0.052</td>
</tr>
<tr>
<td>Genotype 4</td>
<td>480</td>
<td>100 [88.8-100]</td>
<td>98.9 [97.1-99.7]</td>
<td>93.4</td>
<td>100</td>
<td>0.99 [0.99-1.0]</td>
<td>90.9</td>
<td>0</td>
</tr>
</tbody>
</table>

*Estimated HCV prevalence in Cameroon: 13.8%
Results: false results

- 32 wrong results (3.2%) : 22 false negative (FN) and 10 false positive (FP)

- FN compared to TP
  - HCV viral load significantly lower:
    => \( \bar{m} = 32\,851 \text{ UI/mL} \) vs \( \bar{m} = 1\,992\,335 \text{ UI/mL} \) \((p<0.00001)\)
  - Percentage of women significantly lower:
    => 22.7% vs 52.2% \((p=0.007)\)

- FP compared to TN
  - Percentage of HIV-infected sera significantly higher:
    => 60% vs 11.8% \((p<0.0001)\)
Conclusion

• High performance
• No influence of genotype
• No influence of HBV and HIV infection on the overall performance
• Lower specificity in HIV-infected patients
• Reliable diagnostic tool

• Limits: not a study in real world setting => feasibility?

• Perspective: assessment of the performance of AgC quantification as a monitoring tool of HCV antiviral therapy
Perspective: Which role for AgC in hepatitis C diagnosis and screening?

• Unique diagnosis test or confirmatory test?
• Test available only on a specific Abbott platform
• Need for a POC test
• Alternative solution: use of DBS technique + laboratory test
  => BUT lower AgC quantification performance
• Need for screening strategy evaluation

1 Chevaliez, J Infect Dis., 2015
Thank you for your attention