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2016-03-03


http://hdl.handle.net/10138/158948
https://doi.org/10.3109/00365521.2015.1087588

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Introduction

Recently major improvements in efficacy and side effects have been reported regarding treatment for hepatitis C virus (HCV) infection following the introduction of direct antiviral agents (DAAs) [1–4]. This holds true especially for HCV genotype 1, 2 and 4 infections, where interferon-sparing regimens yield high rates of sustained virological response (SVR) with side effect profiles often compatible with placebo. However, with regards to treatment of HCV genotype 3 infection, outcome following DAA-based therapy thus far surprisingly has been poor. When given 12 weeks of sofosbuvir and ribavirin therapy, significantly lower SVR rates were achieved among patients infected with HCV genotype 3 as compared with genotype 2, both among treatment-naïve as well as treatment experienced patients [1,2]. These SVR rates were augmented upon prolongation of treatment duration, but despite 24 weeks of sofosbuvir and ribavirin, only 60% (27 of 45) of treatment-experienced cirrhotic genotype 3 infected patients achieved SVR [5]. When genotype 3 infected cirrhotic patients were treated for 12 weeks with daclatasvir and sofosbuvir without the addition of ribavirin in the phase III ALLY-3 study, only 70% (21 of 30) achieved undetectable HCV RNA four weeks after discontinuation of therapy, i.e. SVR4, in contrast to 94%
therapy with pegylated interferon-
3 infected patients achieve SVR following 24 weeks of
mind that approximately 80% of HCV genotype 2 or
merit therapeutic intervention. It is important to bear in
ments, on a global perspective, health economics likely
will mandate the continued use of interferon-based
therapy as a therapeutic option for several years to
come, especially for patients with less advanced liver
fibrosis, even in more affluent regions [8]. Currently
these patients are not prioritized for DAA-based therapy,
and often are left waiting for possible future reductions
in treatment cost, or progression of fibrosis that would
merit therapeutic intervention. It is important to bear in
mind that approximately 80% of HCV genotype 2 or
3 infected patients achieve SVR following 24 weeks of
therapy with pegylated interferon-α (pegIFN-α) and
ribavirin combination therapy [9], albeit with consider-
able side effects which hampers adherence.

Generally a larger proportion of patients will tolerate
interferon-based combination therapy for 12 rather than
24 weeks [10]. In the previously reported NORDynamIC
trial, with 13% of enrolled patients having liver biopsy
verified cirrhosis, 56% of genotype 2 and 58% of
genotype 3 infected treatment-naive patients achieved
SVR following 12 weeks of therapy with pegIFN-α2a
180 μg weekly and ribavirin 800 mg daily [10]. When
restricting this analysis to patients younger than 40 years,
80% achieved SVR following 12 weeks of therapy [10].
These findings subsequently have been incorporated into
the Finnish HCV treatment guidelines [11], where
patients infected with HCV genotype 2 or 3 below the
age of 40 years are recommended 12 weeks of interferon
and ribavirin combination therapy, whereas patients 40
years or above are offered therapy for 24 weeks.

Aside from age below 40, in the NORDynamIC study,
achieving HCV RNA <1000 IU/mL by day 7, i.e. immedi-
aply prior to the second dose of peg-IFN, entailed
achieving SVR in 92% patients treated for 12 weeks
(ITT-analysis), and was superior to undetectable HCV RNA
week 4, i.e. rapid virological response (RVR), for predicting
favorable outcome [10,12,13]. Consequently both of
these two favorable response factors, i.e. age below 40
or HCV RNA below 1000 IU/mL day 7, have been
incorporated into the Swedish HCV treatment guidelines
[14] as suitable for selection of potential candidates for
shortened treatment duration, i.e. 12–16 weeks, among
genotype 2 or 3 infected patients, provided that no dose
reductions are required and RVR is achieved.

Recently, variants of the inosine triphosphate pyr-
ophosphatase (ITPase) gene (ITPA), which protect
against ribavirin-induced hemolytic anemia during ther-
apy for HCV [15], were reported to be significantly
associated with a ribavirin-like reduction of relapse risk
in the setting of the abovementioned NORDynamIC
study [16,17]. Subsequently this association between
ITPA variants and SVR also has been reported among
HCV genotype 1–4 infected patients treated with higher
ribavirin doses [18].

The aim of the present study was to perform a post-hoc,
re-evaluation of the potential clinical utility of combina-
tions of favorable response predictors, including the
recently reported ITPA variants, following 12 weeks of
interferon and ribavirin therapy for treatment-naive
patients with chronic HCV genotype 2 or 3 infection in
the experimental phase III NORDynamIC trial (n = 382),
analyzing the results for HCV genotypes 2 and 3 infected
patients separately instead of together as previously
reported [10], as well as verifying the therapeutic
outcome among real-life Finnish and Swedish HCV
 genotype 2 or 3 infected patients treated with short
duration interferon-based therapy in accordance with
respective national guidelines. The goal of this assess-
ment was to identify HCV genotype 2 or 3 infected
patients with a high likelihood of achieving SVR following
a shorter course of interferon-based therapy, as patients
with mild fibrosis currently are not candidates for signifi-
cantly more costly interferon-free, DAA-based therapy.

Materials and methods

Patients

NORDynamIC

Three hundred and eighty-two treatment naïve HCV
genotype 2 or 3 infected patients were included in a
phase III, open label, randomized, multicenter, investi-
gator-initiated trial (NORDynamIC) conducted at 31
centers in Denmark, Finland, Norway, and Sweden [10].
All patients were adults with compensated liver disease
and had detectable HCV RNA. At study entry, patients
were randomized to either 12 or 24 weeks of treatment
with 180 μg of peg-interferon α2a once weekly and
800 mg/day ribavirin. Patients having received at least
80% of the target dose of peg-interferon as well as at
least 80% of the target dose of ribavirin for at least 80% of
the target treatment duration (n = 285), were defined
as constituting the per-protocol (PP) population.
Adherence was monitored both by reporting of dose
reductions and missed doses in the case report forms
(CRF) and in the patient diaries in which patients
recorded each dosing. The two patients enrolled who
were simultaneously infected with both HCV genotypes 2 and 3 were excluded from this study, as HCV genotypes 2 and 3 were analyzed separately.

**Real-life patients in Finland**

Between January 2007 and December 2013, 115 HCV genotype 2 infected and 333 HCV genotype 3 infected patients were treated with pegIFN and 800 mg daily dosing of ribavirin at Helsinki University Hospital. Patients below the age of 40 years received 12 weeks of therapy unless they had unfavorable prognostic factors e.g. pronounced steatosis, obesity, metabolic syndrome or cirrhosis. Patients older than 40 years, and those unfavorable pretreatment prognostic factors were treated for 24 weeks.

**Real-life patients in Sweden**

An inquiry was initially performed among tertiary treatment centers in Sweden, and seven centers (Gothenburg, Karlstad, Gävle, Borås, Skövde, Trollhättan and Halmstad) reported that they had offered a total of 32 HCV genotype 2, and 85 HCV genotype 3 infected patients short course treatment as of December 2013. These patients were selected on the basis of age below 40 years and/or achieving HCV RNA below 1000 IU/mL day 7. One center (Halmstad) prescribed 800 mg daily dosing of ribavirin, and the remaining six centers used 11 mg/kg per day dosing. Two centers (Gothenburg and Karlstad) treated patients for 12 weeks, whereas the remaining five gave most often 12 or on rare occasions 16 weeks of therapy.

**The NORDynamIC-study patients**

**ITPA genotyping methods**

SNPs were determined in plasma by allelic discrimination using TaqMan SNP Assays (Life Technologies, Carlsbad, CA): Assay ID C_29168507_10 for rs7270101, and C_27465000_10 for rs1127354. Both SNPs were in Hardy–Weinberg equilibrium.

**Classification of predicted ITPase activity**

This was achieved based on the compound genotype of rs1127354 and rs7270101 as previously determined by biochemical analyses [19–21] (detailed in Table I), i.e. 100% (CC<sub>rs1127354</sub> AA<sub>rs7270101</sub>), 60% (CC<sub>rs1127354</sub> AC<sub>rs7270101</sub>), 30% (CC<sub>rs1127354</sub> CC<sub>rs7270101</sub>), 25% (CA<sub>rs1127354</sub> AA<sub>rs7270101</sub>), 10% (CA<sub>rs1127354</sub> AC<sub>rs7270101</sub>) and <5% (AA<sub>rs1127354</sub> AA<sub>rs7270101</sub>).

**IL28B genotyping**

DNA samples were genotyped for the rs12979860 polymorphism with TaqMan SNP genotyping assays (Applied Biosystems Inc., Foster City, CA), using the ABI 7500 Fast real time thermocycler, according to manufacturers recommended protocols. TaqMan probes and primers were designed and synthesized by Applied Biosystems Inc.

**IP-10 quantification in plasma**

Quantification of IP-10 was performed using Quantikine (R&D SYSTEMS, Minneapolis, MN), a solid-phase ELISA, on plasma samples obtained during the week prior to the start of therapy. All samples were stored at −70°C until assayed.

**HCV RNA quantification**

Plasma HCV RNA was determined using Cobas AmpliPrep/COBAS TaqMan HCV Test (Roche Diagnostics, Branchburg, NJ), which quantifies HCV RNA with a limit of detection of 15 IU/mL. Quantification was performed on days 0, 3, 7, 8, 29, week 8, week 12, week 24 and 24 weeks after completion of therapy. All samples were frozen (−70°C) and centrally analyzed. Patients were classified as achieving SVR if plasma HCV RNA was undetectable 24 weeks after completion of therapy.

**Liver biopsies**

Liver biopsies were obtained from all patients within 24 months prior to study entry. The evaluation was performed in a blinded fashion according to the Ishak protocol [22]. Additionally steatosis was graded [23].

**Statistical methods**

All statistical analyses were performed by SN using IBM SPSS statistics version 19.0 software package (IBM Corporation, Somers, NY). All reported p-values are two-sided, and p-values <0.05 were considered significant.

**Ethical considerations**

Written informed consent was obtained from each participating patient, and ethics committees in each participating country approved the NORDynamIC study. The study has been registered at the NIH trial registry (ClinicalTrials.gov Identifier: NCT00143000). Ethics committees in Gothenburg, Sweden, and Helsinki, Finland.
Table I. Sensitivity, specificity, positive and negative predictive values of various markers on the likelihood of achieving SVR in patients with HCV genotype 2 (n = 50) and genotype 3 (n = 111) included in the per-protocol analysis treated for 12 weeks.

<table>
<thead>
<tr>
<th></th>
<th>Genotype 2</th>
<th>Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Age&lt;40 years</td>
<td>31%</td>
<td>95%</td>
</tr>
<tr>
<td>41% of patients (66/161)</td>
<td>(9/29)</td>
<td>(20/21)</td>
</tr>
<tr>
<td>ITPase activity&lt;100%</td>
<td>57%</td>
<td>90%</td>
</tr>
<tr>
<td>35% of patients (54/154)</td>
<td>(16/28)</td>
<td>(18/20)</td>
</tr>
<tr>
<td>IL28B genotype (CC vs. CT/TT)</td>
<td>54%</td>
<td>43%</td>
</tr>
<tr>
<td>27% of patients (43/161)</td>
<td>(7/29)</td>
<td>(20/21)</td>
</tr>
<tr>
<td>Non-significant fibrosis</td>
<td>46%</td>
<td>58%</td>
</tr>
<tr>
<td>(Ishak stage 0–2)</td>
<td>(13/28)</td>
<td>(11/19)</td>
</tr>
<tr>
<td>50% of patients (74/149)</td>
<td>93%</td>
<td>21%</td>
</tr>
<tr>
<td>Non-cirrhosis (Ishak stage 0–4)</td>
<td>(26/28)</td>
<td>(4/19)</td>
</tr>
<tr>
<td>90% of patients (134/149)</td>
<td>64%</td>
<td>58%</td>
</tr>
<tr>
<td>No steatosis (Steatosis grade 0)</td>
<td>(18/28)</td>
<td>(11/19)</td>
</tr>
<tr>
<td>38% of patients (57/149)</td>
<td>36%</td>
<td>47%</td>
</tr>
<tr>
<td>IP-10 baseline &lt;150 pg/mL</td>
<td>36%</td>
<td>47%</td>
</tr>
<tr>
<td>44% of patients (66/151)</td>
<td>(10/28)</td>
<td>(9/19)</td>
</tr>
<tr>
<td>IP-10 baseline &lt;600 pg/mL</td>
<td>93%</td>
<td>11%</td>
</tr>
<tr>
<td>HCV RNA day 7 &lt;1000 IU/mL</td>
<td>36%</td>
<td>100%</td>
</tr>
<tr>
<td>26% of patients (39/150)</td>
<td>(10/28)</td>
<td>(21/21)</td>
</tr>
<tr>
<td>HCV RNA undetectable week 4 (RVR)</td>
<td>74%</td>
<td>43%</td>
</tr>
<tr>
<td>62% of patients (98/158)</td>
<td>(22/29)</td>
<td>(9/21)</td>
</tr>
<tr>
<td>Age&lt;40 years or HCV RNA day 7 &lt;1000 IU/mL</td>
<td>57%</td>
<td>95%</td>
</tr>
<tr>
<td>52% of patients (82/158)</td>
<td>(16/28)</td>
<td>(20/21)</td>
</tr>
<tr>
<td>Age&lt;40 years and RVR</td>
<td>24%</td>
<td>95%</td>
</tr>
<tr>
<td>27% of patients (43/161)</td>
<td>(7/29)</td>
<td>(20/21)</td>
</tr>
<tr>
<td>Age &gt;40 years and HCV RNA day 7 &lt;1000 IU/mL</td>
<td>25%</td>
<td>100%</td>
</tr>
<tr>
<td>10% of patients (16/158)</td>
<td>(7/28)</td>
<td>(21/21)</td>
</tr>
<tr>
<td>Age&lt;40 years or IL28B genotype CC vs. CT/TT</td>
<td>79%</td>
<td>85%</td>
</tr>
<tr>
<td>HCV RNA day 7 &lt;1000 IU/mL</td>
<td>(22/28)</td>
<td>(17/20)</td>
</tr>
<tr>
<td>65% of patients (102/156)</td>
<td>600 pg/mL</td>
<td>93%</td>
</tr>
<tr>
<td>150 pg/mL</td>
<td>36%</td>
<td>47%</td>
</tr>
<tr>
<td>1000 IU/mL</td>
<td>36%</td>
<td>100%</td>
</tr>
<tr>
<td>(16/28)</td>
<td>(20/21)</td>
<td>(16/17)</td>
</tr>
<tr>
<td>1000 IU/mL (16/28)</td>
<td>(7/29)</td>
<td>(20/21)</td>
</tr>
</tbody>
</table>

have approved the reporting of real-life data from routine clinical patients.

Results

The impact of baseline variables such as age, ITPase activity, liver fibrosis, steatosis, IL28B genotype and baseline IP-10, and on-treatment HCV RNA levels day 7 and week 4, as well as combination thereof on outcome following 12 weeks of combination therapy in the NORDynamIC trial were re-evaluated separately for HCV genotypes 2 and 3 (PP analysis in Table I). The highest positive predictive values were noted for HCV RNA <1000 IU/mL day 7, which was achieved by 26% of enrolled patients (Figure 1), closely followed by age below 40 years (Figure 2), and approximately half of all patients fulfilled either of these criteria. More than 80% of both genotype 2 and 3 infected patients fulfilling these criteria, subsequently achieved SVR both in intention-to-treat and PP analyses. If ITPase activity <100% also was included, 65% of patients fulfilled any of these criteria, however, the SVR rate among adherent, HCV genotype 3 infected patients was below 80% (Table I).

Since 2007, duration of pegIFN-α and ribavirin therapy for HCV genotype 2/3 infection mainly has been determined by age in Finland, with patients younger than 40 years being treated for 12 weeks in contrast to patients above 40 years, who received 24 weeks of treatment (Table II). Interestingly, Finnish patients infected with HCV genotype 2 were more likely to be above 40 years of age as compared to genotype 3 (59% vs 40 years for genotype 2 vs. 38% for genotype 3, respectively; p < 0.0001, Chi-squared), similar to what has previously been reported among the patients enrolled in the NORDynamIC study (mean age 47.2 vs. 39.8 years for genotypes 2 and 3, respectively; p < 0.0001 Mann–Whitney U-test) [10]. Also a significantly higher proportion of patients below 40 years of age achieved SVR than older patients in spite of being prescribed only half the treatment duration (81% vs. 73% for patients <40 vs. >40 years of age respectively; p = 0.039, Chi-squared). A non-significant trend was also noted towards greater likelihood of achieving SVR among patients infected...
with HCV genotype 2 vs. 3 (83% vs. 75% for genotypes 2 and 3, respectively). It should be noted that Finnish HCV genotype 2/3 infected patients generally received 800 mg daily flat dosing of ribavirin.

In Sweden, seven centers reported that they routinely offered HCV genotype 2/3 infected patients younger than 40 years of age and/or those achieving <1000 IU/mL day 7 pegIFN-α and ribavirin combination therapy for 12–16 weeks. Among HCV genotype 2 infected patients, 97% achieved SVR, and among genotype 3 infected, 94% achieved SVR (Table III).

**Discussion**

The results of this study of both experimental clinical trial and confirming real-life data suggest that combinations of both baseline patient characteristics and/or on-treatment responses can select for suitable HCV genotype 2 or
3 infected candidates with a high likelihood of achieving SVR after as short as 12 weeks of interferon-based combination therapy. From a clinical perspective, baseline factors may be preferential as they do not require initiation of therapy. To this end, age below 40 years is an attractive selective characteristic as it does not require laboratory analyses, and allows for the discussion of short course interferon-based therapy at an early time-point after referral to a tertiary treatment center. HCV RNA below 1000 IU/mL was the best predictor of subsequently achieving SVR, especially among adherent patients, but obviously requires initiation of therapy.

Although the number of Swedish patients offered short-duration treatment thus far has been substantially lower than in Finland, slightly higher SVR rates have been achieved. This possibly could be due to more frequent use of higher, weight-based ribavirin dosing (11 mg/kg weight per day), occasional prolongation of treatment duration to 16 weeks, or more restrictive selection of candidates deemed suitable, e.g. the provision that no dose reductions are performed and RVR is achieved. Additionally, the Finnish patient population included those with advanced liver fibrosis, which also may have contributed to the lower SVR rates achieved. However, it is important to bear in mind that the general use of higher, weight-based ribavirin dosing as compared to 800 mg daily dosing will entail more side effects, primarily anemia.

The side effects of interferon-based combination therapy are substantially more common and severe than those associated with interferon-free DAA regimens, and must be discussed with patients prior to initiation of therapy as they may negatively impact both on work and social life. Many side effects, however, debut after 12 weeks of therapy, and thus can be avoided by shorter duration. Unfortunately, neuropsychiatric symptoms such as depression often appear as early as after two weeks [24]. The impact of these side effects, however, can be ameliorated by routine monitoring using standardized questionnaires, and early intervention [24]. The management of these side effects demands additional laboratory monitoring and resources of health-care providers, as well as other incremental costs, e.g. sick leave. These issues impact on the cost-effectiveness of interferon-based as compared to DAA-based therapy. However, because of the substantial costs of DAA-based regimens, these treatment options often are reserved for cirrhotic and pre-cirrhotic patients. Thus, patients with mild fibrosis currently are unlikely to be candidates for DAA-based therapy, and in this light, 12 weeks of interferon-based treatment may be attractive for some easy-to-cure HCV genotype 2/3 infected patients with favorable characteristics despite potential side effects.

In conclusion, the results of this study suggest that as short as 12 weeks of interferon and ribavirin therapy is an acceptable alternative for selected HCV genotype 2/3 infected patients, given that a thorough discussion of the potential side effects is provided prior to initiation.

Table II. Real-Life SVR data among Finish HCV genotype 2/3 infected patients where duration is determined by age; Ribavirin 800 mg per day.

<table>
<thead>
<tr>
<th>Year</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;40 years</td>
<td>≥40 years</td>
</tr>
<tr>
<td>2007</td>
<td>9 of 9 (100%)</td>
<td>8 of 9 (89%)</td>
</tr>
<tr>
<td>2008</td>
<td>9 of 11 (82%)</td>
<td>2 of 4 (50%)</td>
</tr>
<tr>
<td>2009</td>
<td>9 of 10 (80%)</td>
<td>11 of 13 (85%)</td>
</tr>
<tr>
<td>2010</td>
<td>2 of 2 (100%)</td>
<td>9 of 14 (64%)</td>
</tr>
<tr>
<td>2011</td>
<td>1 of 1 (100%)</td>
<td>7 of 7 (100%)</td>
</tr>
<tr>
<td>2012</td>
<td>5 of 6 (83%)</td>
<td>9 of 9 (100%)</td>
</tr>
<tr>
<td>2013</td>
<td>7 of 8 (88%)</td>
<td>8 of 12 (67%)</td>
</tr>
<tr>
<td>Total</td>
<td>41 of 47 (87%)</td>
<td>54 of 68 (79%)</td>
</tr>
</tbody>
</table>

Table III. Real-life SVR data among Swedish genotype 2/3 infected patients achieving <1000 IU/mL day 7 or age <40 years treated for 12–16 weeks.

<table>
<thead>
<tr>
<th>Center</th>
<th>HCV genotype 2</th>
<th>HCV genotype 3</th>
<th>Ribavirin dosing</th>
<th>Treatment duration</th>
<th>Criteria for patient selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gothenburg</td>
<td>6 of 6</td>
<td>16 of 17</td>
<td>11 mg/kg per day</td>
<td>12 weeks</td>
<td>&lt;1000 IU/mL day 7 or &lt;40 years</td>
</tr>
<tr>
<td>Karlstad</td>
<td>5 of 5</td>
<td>5 of 6</td>
<td>11 mg/kg per day</td>
<td>12 weeks</td>
<td>&lt;1000 IU/mL day 7</td>
</tr>
<tr>
<td>Gävle</td>
<td>6 of 6</td>
<td>19 of 19</td>
<td>11 mg/kg per day</td>
<td>12–16 weeks</td>
<td>&lt;1000 IU/mL day 7</td>
</tr>
<tr>
<td>Borås</td>
<td>7 of 8</td>
<td>9 of 10</td>
<td>11 mg/kg per day</td>
<td>12–16 weeks</td>
<td>&lt;1000 IU/mL day 7</td>
</tr>
<tr>
<td>Skövde</td>
<td>2 of 2</td>
<td>18 of 20</td>
<td>11 mg/kg per day</td>
<td>12–16 weeks</td>
<td>&lt;1000 IU/mL day 7 or &lt;40 years</td>
</tr>
<tr>
<td>Trollhättan</td>
<td>3 of 3</td>
<td>10 of 10</td>
<td>11 mg/kg per day</td>
<td>12–16 weeks</td>
<td>&lt;1000 IU/mL day 7</td>
</tr>
<tr>
<td>Halmstad</td>
<td>2 of 2</td>
<td>3 of 3</td>
<td>800 mg daily</td>
<td>12–16 weeks</td>
<td>&lt;1000 IU/mL day 7 or &lt;40 years</td>
</tr>
<tr>
<td>Total</td>
<td>31 of 32 (97%)</td>
<td>80 of 85 (94%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Acknowledgements

We thank Anne-Sofie Tylö, Marie-Louise Landelius, Jenny Hende, and Ulla Gingsjö for expert technical assistance.

Declaration of interest

None of the authors have an association that might pose a conflict of interest.

The Swedish Medical Research Council and ALF Funds at Sahlgrenska University Hospital supported this study. Unrestricted grants from Roche affiliates in the Nordic region also supported the NORDynamIC study, but not the collection of real-life data. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References