Direct-acting antiviral therapy for chronic hepatitis C
de Bruijne, J.

Citation for published version (APA):
de Bruijne, J. (2012). Direct-acting antiviral therapy for chronic hepatitis C
First-in-Human Pharmacokinetics and Antiviral Activity of IDX375, a Novel Non-Nucleoside Hepatitis C Virus Polymerase Inhibitor

Joep de Bruijne, Jeroen van de Wetering de Rooij, Andre A. van Vliet, Xiao-Jian Zhou, Marie-Francoise Temam, Jeffrey Molles, Jie Chen, Keith Pietropaolo, John Z. Sullivan-Bólyai, Douglas Mayers, Hendrik W. Reesink

Antimicrobial Agents Chemotherapy 2012, accepted
Background: IDX375 is a potent and selective palm-binding non-nucleoside inhibitor of the HCV genotype-1 polymerase. This first-in-human study evaluated the safety, tolerability and pharmacokinetics of IDX375 in healthy volunteers as well as antiviral activity in HCV-infected patients.

Methods: IDX375 as a choline salt was administered for one day to forty healthy male volunteers (25-200 mg IDX375-equivalent single-ascending doses and a 200 mg twice-daily [BID] dose) and three patients chronically infected with HCV genotype-1 (200 mg BID only).

Results and Conclusion: IDX375 was well-absorbed and well-tolerated in all study participants. A single-day 200 mg BID dose resulted in exposure-related anti-HCV activity with maximal 0.5-1.1 log10 reductions in plasma HCV RNA. These observations support further clinical investigations of IDX375.

IDX375 (Figure 1) is a potent and selective palm-binding NNI of the HCV genotype-1 polymerase. This compound demonstrated low nanomolar potency in vitro (EC50 = 2.3 nM) in the HCV genotype-1b replicon with a selectivity index of >43,000.7 IDX375 has about 2.7-fold less activity against the genotype-1a replicon, which is in the 2-3 fold range typically seen with most of the other NNIs currently under clinical evaluation.8-12 The exception is ANA598 which has a 17-fold less activity against genotype 1a.13 Treatment of replicon cells with 20× EC50 of IDX375 for 14 days resulted in a 3 log10 reduction in HCV replicon RNA and reduced the number of replicon-containing foci in cell culture.7 IDX375 was not cytotoxic against a series of test cell lines. The pharmacokinetic profile of IDX375 in several animal species showed adequate plasma drug exposure with bioavailability ranging from 16% to 42%, as well as high liver concentrations.7,14 Standard preclinical safety assessments demonstrated that IDX375 is not genotoxic, tested negative in the hERG assay and had no significant central nervous, cardiovascular, respiratory, gastrointestinal or renal effects/findings. Toxicology evaluations supported the 25 mg starting dosing in human with a safety margin up to 100 fold (unpublished data). The objectives of this first-in-human study were to evaluate the safety, tolerability, and pharmacokinetics of IDX375 as a choline salt in healthy male volunteers following single ascending-doses as well as antiviral activity in patients with HCV genotype-1 infection following a single-day dose.15 This study was conducted in accordance with Good Clinical Practice procedures, the principles of the Declaration of Helsinki, and regulations from regulatory authorities. Clinical conduct took place at Pharmaceutical Research Associates Group (Zuidlaren, The Netherlands) and HCV-
This study was approved by Ethics Committees from the participating trial centers. All subjects gave written informed consent before any study related activity. Forty healthy male volunteers were enrolled in the dose escalation part while three (two male and one female) HCV-infected patients were also enrolled. As shown in Table 1, subjects were predominantly Caucasians; treatment cohorts were comparable with respect to baseline characteristics. All patients were infected with HCV genotype-1a and were non-responders to previous IFN-based treatment. Individual baseline HCV RNA levels were 6.0, 6.3 and 7.6 log_{10} IU/mL. Two healthy volunteers, one on placebo and the other on active IDX375, received acetaminophen for toothache (once) and muscle pain (PRN). The HCV-infected patients were allowed to continue on their stable medications including methadone (see below).

### Table 1. Plasma pharmacokinetic parameters of IDX375 in healthy subjects and HCV-infected patients.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>No. of subjects</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (µg/mL×h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>C&lt;sub&gt;τ&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>6</td>
<td>0.16±0.04</td>
<td>4.0 (2.0-4.0)</td>
<td>5.16±1.16</td>
<td>42.3±8.60</td>
<td>0.05±0.01</td>
</tr>
<tr>
<td>50</td>
<td>6</td>
<td>0.42±0.08</td>
<td>1.0 (1.0-4.0)</td>
<td>12.0±3.16</td>
<td>34.3±8.8</td>
<td>0.11±0.03</td>
</tr>
<tr>
<td>100</td>
<td>6</td>
<td>0.98±0.78</td>
<td>4.0 (4.0-6.0)</td>
<td>13.9±5.79</td>
<td>32.6±6.40</td>
<td>0.13±0.04</td>
</tr>
<tr>
<td>200</td>
<td>6</td>
<td>3.83±2.89</td>
<td>4.0 (3.0-6.0)</td>
<td>29.4±15.7</td>
<td>32.5±7.20</td>
<td>0.24±0.14</td>
</tr>
</tbody>
</table>

Twice-daily for one day

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>No. of subjects</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (µg/mL×h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>C&lt;sub&gt;τ&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 am</td>
<td>6</td>
<td>2.38±1.34</td>
<td>4.0 (3.0-6.0)</td>
<td>46.8±7.37</td>
<td>31.0±7.70</td>
<td>0.49±0.14</td>
</tr>
<tr>
<td>200 pm</td>
<td>6</td>
<td>4.12±1.80</td>
<td>8.0 (8.0-12)</td>
<td>46.8±7.37</td>
<td>31.0±7.70</td>
<td>2.10±1.07</td>
</tr>
</tbody>
</table>

Twice-daily for one day in HCV-infected patients

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>No. of subjects</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (µg/mL×h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>C&lt;sub&gt;τ&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 am</td>
<td>3</td>
<td>4.44±2.61</td>
<td>4.0 (4.0-4.0)</td>
<td>172 ± 107</td>
<td>36.4±4.10</td>
<td>1.85±1.22</td>
</tr>
<tr>
<td>200 pm</td>
<td>3</td>
<td>7.95±4.62</td>
<td>12 (12 - 12)</td>
<td>172 ± 107</td>
<td>36.4±4.10</td>
<td>7.95±4.62</td>
</tr>
</tbody>
</table>

Single IDX375-equivalent doses of 25, 50, 100 and 200 mg and a single-day 200 mg BID dose of IDX375 were sequentially administered with food to five cohorts of healthy male volunteers (IDX375 choline salt doses from 30 mg to 480 mg per day). The 25 mg and 50 mg doses were sequentially administered with food to five cohorts of healthy male volunteers. The 25 mg and 50 mg doses were sequentially administered with food to five cohorts of healthy male volunteers.IDX375-equivalent doses of 25, 50, 100 and 200 mg and a single-day 200 mg BID dose of IDX375 were sequentially administered with food to five cohorts of healthy male volunteers.IDX375-equivalent doses of 25, 50, 100 and 200 mg and a single-day 200 mg BID dose of IDX375 were sequentially administered with food to five cohorts of healthy male volunteers.

All subjects completed the study and were included in the analyses. IDX375 was well tolerated in healthy volunteers and HCV-infected patients at doses up to 200 mg BID for one day. There were no serious adverse events, dose-limiting toxicities or patterns suggesting IDX375-related adverse events (AEs) or abnormalities in vital signs or electrocardiograms. The frequency of AEs across active treatment groups in healthy volunteers was low and comparable to placebo. The most common AE in healthy volunteers receiving IDX375 was diarrhea (3/30 subjects), while dry lips (3/3 subjects) and dysgeusia (2/3 subjects) were most common in HCV-infected patients. All AEs were mild in intensity. Figure 2 depicts mean (+SD) plasma concentration vs. time profiles. Table 2 summarizes plasma pharmacokinetics.IDX375 was well absorbed upon oral dosing with dose-related exposure within the studied single dose range, which extended to 400 mg/day (200 mg BID) in healthy volunteers based on total exposure (AUC<sub>τ</sub>). With BID dosing in healthy volunteers and patients, the maximum (C<sub>max</sub>) and trough (C<sub>τ</sub>) concentrations associated with the evening dose were about 2-fold and 4-fold the morning dose, respectively.
PART I - Drugs interacting with the hepatitis C virus life cycle

Pharmacokinetics and antiviral activity of IDX375 - CHAPTER 6

HCV-infected patients had higher plasma exposure of IDX375 with 2-fold mean Cmax and 4-fold mean AUC∞ compared to healthy volunteers (Figure 2, lower panel; Table 2). Two of the three patients had the highest exposure in the study while the third one had comparable exposure to healthy volunteers. Interestingly, both patients were on methadone maintenance therapy. One of them, the only female participant of the study, also took citalopram for depression. Since CYP3A4 is involved in the metabolism of methadone\textsuperscript{17}, citalopram\textsuperscript{18} as well as IDX375\textsuperscript{14}, drug-drug interactions might therefore be to some extent associated with the elevated exposure observed in these two patients. In addition, HCV-infected patients with potentially impaired liver function relevant to drug metabolism and elimination may have higher plasma exposures of IDX375. Higher exposures in patients compared to healthy volunteers were reported for other DAAIs including the protease inhibitor TMC435.\textsuperscript{16} The small number of HCV-infected patients in the current study and the relatively large variability associated with plasma exposure in patients (approx 60% for Cmax, Cτ, and AUC∞), however, prevented definitive assessment of exposure differences between the two populations. Future trials with a larger number of subjects would shed more light on these initial observations.

Figure 2. Mean ± SD plasma concentration-time profiles of IDX375 following single ascending dosing (upper panel) and twice daily dosing (lower panel).

Consistent with its preclinical pharmacokinetic properties, urine excretion of IDX375 in humans was negligible (< 0.1% of the administered doses). As presented in Figure 3, IDX375 exhibited concentration-dependent antiviral activity in all three patients. With a single-day 200 mg BID dose, maximum individual reductions from baseline in plasma HCV RNA were -0.5, -0.6 and...
Pharmacokinetics and antiviral activity of IDX375 - CHAPTER 6

-1.1 log_{10} Mean morning and evening C exceeded the int vitro protein binding-adjusted EC50 of genotype-1a (~500 ng/mL or ~925 nM) by 4-fold and 15-fold, and genotype 1b (~180 ng/mL or ~330 nM) by 10-fold and 40-fold, respectively (unpublished data). Viral replication was suppressed as long as plasma concentration was maintained above approx 1-2 μg/mL. While trough concentrations above this threshold can easily be achieved with once or twice daily dosing, for the same total daily dose, a twice daily dosing regimen is preferred for being able to maintain trough exposure and avoiding high Cmax which could be associated with elevated bilirubin as described below.

IDX375 is an inhibitor of the uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) with an in vitro IC50 of approx 7 μg/mL or ~13 μM (unpublished data). In the current study, while no subject experienced abnormal changes in bilirubin levels, the two HCV-infected patients who had the highest plasma IDX375 concentrations had slight increases in total bilirubin which appeared to be driven by an increase in indirect bilirubin. These increases were consistent with UGT1A1 inhibition and were asymptomatic without associated increases in alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase. There were no patterns suggestive of IDX375-related effects noted for other laboratory parameters. In summary, IDX375 dosed up to 400 mg for one day was well tolerated without dose-limiting toxicity. A 200 mg BID dose of IDX375 for one day resulted in exposure dependent antiviral activity in patients infected with HCV genotype-1. These initial observations support further clinical investigations of IDX375 at higher doses with longer duration.

REFERENCES

7. Chauret N, C Chagnon-Labelle, M Diallo, et al. Mean morning and evening C exceeded the in vitro protein binding-adjusted EC50 of genotype-1a (~500 ng/mL or ~925 nM) by 4-fold and 15-fold, and genotype 1b (~180 ng/mL or ~330 nM) by 10-fold and 40-fold, respectively (unpublished data). Viral replication was suppressed as long as plasma concentration was maintained above approx 1-2 μg/mL. While trough concentrations above this threshold can easily be achieved with once or twice daily dosing, for the same total daily dose, a twice daily dosing regimen is preferred for being able to maintain trough exposure and avoiding high Cmax which could be associated with elevated bilirubin as described below.

IDX375 is an inhibitor of the uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) with an in vitro IC50 of approx 7 μg/mL or ~13 μM (unpublished data). In the current study, while no subject experienced abnormal changes in bilirubin levels, the two HCV-infected patients who had the highest plasma IDX375 concentrations had slight increases in total bilirubin which appeared to be driven by an increase in indirect bilirubin. These increases were consistent with UGT1A1 inhibition and were asymptomatic without associated increases in alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase. There were no patterns suggestive of IDX375-related effects noted for other laboratory parameters. In summary, IDX375 dosed up to 400 mg for one day was well tolerated without dose-limiting toxicity. A 200 mg BID dose of IDX375 for one day resulted in exposure dependent antiviral activity in patients infected with HCV genotype-1. These initial observations support further clinical investigations of IDX375 at higher doses with longer duration.

REFERENCES

7. Chauret N, C Chagnon-Labelle, M Diallo, et al. Mean morning and evening C exceeded the in vitro protein binding-adjusted EC50 of genotype-1a (~500 ng/mL or ~925 nM) by 4-fold and 15-fold, and genotype 1b (~180 ng/mL or ~330 nM) by 10-fold and 40-fold, respectively (unpublished data). Viral replication was suppressed as long as plasma concentration was maintained above approx 1-2 μg/mL. While trough concentrations above this threshold can easily be achieved with once or twice daily dosing, for the same total daily dose, a twice daily dosing regimen is preferred for being able to maintain trough exposure and avoiding high Cmax which could be associated with elevated bilirubin as described below.

IDX375 is an inhibitor of the uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) with an in vitro IC50 of approx 7 μg/mL or ~13 μM (unpublished data). In the current study, while no subject experienced abnormal changes in bilirubin levels, the two HCV-infected patients who had the highest plasma IDX375 concentrations had slight increases in total bilirubin which appeared to be driven by an increase in indirect bilirubin. These increases were consistent with UGT1A1 inhibition and were asymptomatic without associated increases in alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase. There were no patterns suggestive of IDX375-related effects noted for other laboratory parameters. In summary, IDX375 dosed up to 400 mg for one day was well tolerated without dose-limiting toxicity. A 200 mg BID dose ofIDX375 for one day resulted in exposure dependent antiviral activity in patients infected with HCV genotype-1. These initial observations support further clinical investigations ofIDX375 at higher doses with longer duration.