Original article

Rapid decline of viral RNA in chronic hepatitis C patients treated once daily with IDX320: a novel macrocyclic HCV protease inhibitor

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Background: The addition of direct-acting antivirals to pegylated interferon-α plus ribavirin for the treatment of chronic HCV infection can result in an increased sustained viral response rate and may permit reduction in treatment duration. IDX320 is a potent non-covalent macrocyclic inhibitor of the HCV NS3/4A protease.

Methods: This was a randomized double-blind placebo-controlled single- and multiple-dose study to assess the safety, tolerability, antiviral activity and pharmacokinetics of IDX320 in healthy volunteers (HV) and patients with chronic HCV genotype 1 infection. HV (n=48) received single or multiple ascending doses of IDX320. Two HCV-infected patients received a single dose of 200 mg IDX320. Dosages for other HCV-infected patients were as follows: placebo, 50, 100, 200 or 400 mg of IDX320 orally once daily for 3 days (n=30) or placebo/200 mg of IDX320 twice-daily for 3 days (n=8).

Results: In total, 48 HV and 40 HCV-infected patients were enrolled and all completed the study. There were no serious adverse events. The majority of adverse events were of mild or moderate intensity. Pharmacokinetics supported a once-daily dosing regimen. A rapid decline in plasma HCV RNA was observed in all patients. In the multiple-dose study, mean HCV RNA reductions were 2.6, 3.1, 3.1, 3.3 and 3.8 log10 IU/ml after 3 days in the IDX320 50, 100, 200, 400 mg once-daily and 200 mg twice-daily treatment groups, respectively. This compared to a mean HCV RNA reduction of 0.04 log10 in the placebo group.

Conclusions: Once-daily IDX320 dosing demonstrated potent dose-dependent antiviral activity in treatment-naive HCV genotype-1-infected patients.

Introduction

Chronic HCV infection is an important cause of liver fibrosis leading to cirrhosis, end-stage liver disease and the development of hepatocellular carcinoma [1]. Treatment with pegylated interferon (PEG-IFN)-α and ribavirin (RBV), has achieved sustained viral response (SVR) in approximately 45% of patients infected with genotype 1, 50%–60% of genotype 4 patients, and up to 80% of patients infected with genotypes 2 or 3 [2–4]. Emerging data suggest that SVR may be associated with improved long-term clinical outcomes, including increased survival [5].

Most patients tolerate PEG-IFN/RBV poorly and many are not good candidates for this treatment combination due to advanced liver disease or concurrent
medical conditions. Furthermore, those who failed PEG-IFN/RBV have poor SVR rates after retreatment with PEG-IFN/RBV [6,7]. These problems have prompted the development of direct-acting antiviral agents, which, in combination with PEG-IFN/RBV have led to increased cure rates and shorter treatment durations [8].

Direct-acting antivirals, such as first-generation linear NS3 protease inhibitors (telaprevir and boceprevir), have been evaluated in Phase II and III clinical trials in combination with PEG-IFN/RBV [9–14]. The addition of telaprevir has improved SVR for treatment-naive HCV genotype-1-infected patients to 72%. A high proportion achieved undetectable HCV RNA during the first 4 weeks of therapy, enabling response-guided regimens that shorten treatment duration while preserving high SVR rates. The primary disadvantages of telaprevir and boceprevir are development of viral resistance in patients who do not achieve SVR, three times daily administration and additional side effects, such as rash and anaemia [10,11].

IDX320 is a potent macrocyclic HCV NS3/4A protease inhibitor that suppresses viral replication of multiple HCV genotypes in vitro. In biochemical assays, the 50% inhibitory concentration (IC50) in genotypes 1a, 1b, 2a and 4a was 0.8–1.9 nM and in genotype 3a was 23 nM. In a range of human cellular assays, IDX320 inhibited genotype 1a and genotype 1b replicons with low to subnanomolar potency with a 50% effective concentration (EC50) of 3.4 nM (2.7 ng/ml) and 0.5 nM (0.4 ng/ml), respectively [15]. The 90% effective concentration (EC90) was 5.2 nM (4.2 ng/ml) in the genotype 1a replicon and 1.5 nM (1.2 ng/ml) in the genotype 1b replicon (data not shown). These data imply that IDX320 is approximately 100-fold more potent in vitro than telaprevir and boceprevir [16,17]. The replicon data also suggest that combination of IDX320 with IFN-α will enhance HCV RNA reduction and suppress the selection of HCV drug resistance mutations.

The IDX-07A-001 study described here was designed to investigate the safety, tolerability, antiviral activity and pharmacokinetic profile of IDX320 in single and multiple ascending doses in healthy subjects and patients with chronic HCV infection.

Methods

Study design and organization

This was a four-part study designed to assess safety and pharmacokinetics in healthy subjects prior to enrolling HCV-infected patients. The first part (Part A) was a randomized double-blind placebo-controlled sequential dose-escalation in 48 healthy male subjects. Eight subjects per dose level were randomized to receive, in a 6:2 ratio, either IDX320 or matching placebo. Six IDX320 dose levels were explored: a single dose of 50, 100, 200 or 400 mg in the fed state, 400 mg in the fasted state and 400 mg once-daily in the fed state for 3 days. The second part (Part B) was the administration of an open-label single dose of IDX320 200 mg to two HCV-infected patients, either treatment-naive or treatment-experienced, that was initiated after safety reviews from Part A and approval by the ethics committee (Stichting Beoordeling Ethiek Bio-Medisch Onderzoek, Assen, the Netherlands). Patients in the single-dose portion of the study were confined for 5 days after dosing. The third part (Part C) was the administration of multiple ascending doses of IDX320 to parallel groups of treatment-naive HCV genotype-1-infected patients. A total of 30 patients were randomized equally and received either placebo, 50, 100, 200 or 400 mg IDX320 once-daily for 3 days. In the fourth part (Part D), 8 HCV-infected patients were randomized to 200 mg IDX320 (n=6) or placebo (n=2) twice-daily for 3 days. Placebo and IDX320 were administered in the fed state to all patients. After 3 days of IDX320 monotherapy, patients were offered extended therapy with PEG-IFN-α2a (180 µg/week) and weight-based RBV (1,000 or 1,200 mg/day) for up to 48 weeks. Patients were confined for 7 days after dosing and returned for additional follow-up 3–4 weeks after the dosing period. The study was conducted from January 2010 to August 2010. This study was conducted in accordance with Good Clinical Practice and with the World Medical Association Declaration of Helsinki after approval by the ethics committee at each site. All subjects provided written informed consent before participating in any study-related activity.

IDX320 dosing was conducted as an inpatient study; PEG-IFN/RBV was administered on an outpatient basis. Study medication was supplied by Idenix Pharmaceuticals, Inc (Cambridge, MA, USA). IDX320 and matched-placebo were orally administered as 50 mg tablets. Treatment was prepared by designated site pharmacists, who were not involved in the study procedures, assessments or data recording and did not reveal the randomization during the study according to the CONSORT guidelines [18]. Treatment was dispensed in a blinded fashion by study staff for administration to the subjects.

Inclusion criteria of healthy volunteers and hepatitis C patients

To determine eligibility, healthy male volunteers underwent a medical evaluation that included a physical examination, medical history, electrocardiogram, laboratory tests, urinalysis and virus serology testing for HCV, HBV and HIV.

Chronic hepatitis C patients were males and females, between 18 and 65 years, with a body mass index (BMI)
18–35 kg/m², HCV RNA ≥ 5 log₁₀ IU/ml, genotype 1 infection, alanine aminotransferase (ALT) ≤ 5× the upper limit of normal and no other clinically significant laboratory abnormalities. In the single-dose study, inclusion of both IFN treatment-naive and treatment-experienced patients was allowed. Only treatment-naive patients were included in the multiple-dose studies. Key exclusion criteria were decompensated liver disease, Child Pugh B/C liver cirrhosis, hepatocellular carcinoma, and coinfection with HBV or HIV.

Pharmacokinetics

From the single-dose cohorts, serial plasma samples were collected after dosing, followed by daily sampling for 5 days post-dosing. Urine pharmacokinetic samples were collected for 5 days post-dosing. Intensive pharmacokinetic sampling was performed over 24 h after the first and third IDX320 dosing days during the multiple-dose sections, followed by daily sampling for 5 days after the last dose. Non-compartmental analyses were performed to generate principal plasma pharmacokinetic parameters including total exposure (area under the curve [AUC]), maximum concentration (Cmax), time to reach Cmax (Tmax), trough concentrations (Ctrough), C12 h for once daily and C24 h for twice daily) and half-life. Plasma concentrations of IDX320 were determined using a validated liquid chromatographic-tandem mass spectrometric method, with a limit of quantification of 2.0 ng/ml.

Viral assessments

HCV genotype and subtype were determined at screening, using two methods. Genotyping of patients was performed as described by Murphy et al. [19] (Part B) or by using the Versant HCV Genotype Assay 2.0 (LiPA; Siemens, Tarrytown, NY, USA), by sequence analysis of the 5’ non-coding region of HCV (Parts C and D). The genotyping results were subsequently validated by NS3-4A sequence analysis.

Multiple samples for determination of plasma HCV RNA levels were obtained during the IDX320 treatment period and for 5 days post-dosing. In the multiple-dose studies, a sample was also obtained 7 days post-dosing and at the final follow-up visit on day 28. HCV RNA was quantitated by a validated real-time PCR assay (COBAS® TaqMan®; Roche, Pleasanton, CA, USA), with a quantification range of 43–69×10⁴ IU/ml and a lower limit of detection of 15 IU/ml. Genotyping of IL28B single nucleotide polymorphism rs12979860 was determined by direct sequencing [20]. Patients were not randomized or stratified according IL28B genotype.

Viral resistance analysis

In the single-dose study, plasma samples were collected prior to treatment and during 5 days after dosing (Part B). In the multiple ascending-dose study (Parts C and D), plasma samples were collected from all patients prior to treatment, and 1 and 4 days after the final dose for population sequencing (DDL Diagnostic Laboratory, Voorburg, the Netherlands). All samples with a viral load ≥ 1,000 IU/ml were sequenced. RNA was isolated using the QIAGEN MinElute Virus Spin Kit (Qiagen GmbH, Hilden, Germany). The NS3 through NS4A region of the HCV genome was converted into complementary DNA by the Roche Transcriptor kit and amplified by nested PCR using the Expand High Fidelity kit (Roche Diagnostic GmbH, Mannheim, Germany). Purified PCR products were sequenced from both directions using the BigDye® Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA, USA). Sequences were then manually edited and assembled using SeqScape software (Applied Biosystems). When two or more fluorescence signals were obtained at a single nucleotide base position, a mixed base was called if the lowest signal exceeded 25% of the highest signal, as recommended by the software manufacturer.

Safety assessments

All subjects were monitored for safety and tolerability at regular intervals from the start of IDX320 dosing through completion of the follow-up visits. Safety assessments included clinical history, routine laboratory evaluations, physical examination, 12-lead electrocardiograms, vital signs and the recording of all adverse events.

Results

Baseline characteristics of healthy volunteers and hepatitis C patients

A total of 48 healthy subjects and 40 HCV-infected patients were enrolled (Figure 1). Baseline characteristics of healthy volunteers and HCV-infected patients are summarized in Tables 1 and 2, respectively. Demographic characteristics and BMI at baseline were generally comparable across the groups in both healthy subjects and HCV-infected patients, with the exception of age in the healthy volunteers. HCV-infected groups were comparable with regards to HCV RNA and ALT levels. All patients were Caucasian and predominantly infected with HCV genotype 1b. One patient randomized to the 50 mg IDX320 once-daily cohort was incorrectly dosed with 400 mg IDX320 once-daily for 3 days and has been included in the 400 mg once-daily group in the analyses.

Pharmacokinetics of IDX320 in healthy volunteers and chronic hepatitis C patients

Following oral administration of a single ascending dose in healthy subjects under fed conditions, peak and total plasma exposures of IDX320 were less than...
dose-proportional. An eightfold increase in dose, from 50 to 400 mg, led to an approximate threefold to fourfold increase in mean $C_{\text{max}}$ and $AUC_{\infty}$. By contrast, $C_{\text{trough}}$ at 24 h appeared dose-proportional with a 10-fold increase in the studied dose range. Mean $C_{\text{max}}$ was reached at a median $T_{\text{max}}$ of 3 h regardless of dose. Mean terminal half-life was 24–26 h for doses $\geq 100$ mg.

One treatment-naive and one treatment-experienced patient received a single 200 mg dose and their plasma exposures of IDX320 did not appear to be substantively higher compared to healthy subjects considering the variability associated with a small sample size. IDX320 exposure was 2–3-fold higher with food compared to fasting state. Median $T_{\text{max}}$ remained consistent at 3 h.

Similar to the observations in healthy subjects, plasma exposure of IDX320 in HCV-infected patients was less than dose-proportional (Additional file 1). Following repeated once-daily and twice-daily dosing for 3 days, IDX320 did not appear to appreciably accumulate in terms of $C_{\text{max}}$ and $AUC$ considering the associated interindividual variability. The IDX320 mean terminal half-life ranged from 25.2 to 28.9 h in the once-daily dosing groups and was 52.6 h in the twice-daily dosing group. There was a steady increase in $C_{\text{trough}}$ over time. For the same total daily dose, while maintaining comparable peak exposure, trough concentrations were approximately 2 to 3-fold higher with the 200 mg twice-daily dose than with the 400 mg once-daily dose. Overall,

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**Figure 1. Study flow diagram of healthy participants and chronic hepatitis C patients**

(A) Healthy participants. (B) Chronic hepatitis C patients. *These subjects received IDX320 in fasted condition. Participants in all other cohorts received IDX320 with food.*
peak and total plasma exposures of IDX320 in HCV-infected patients and healthy subjects were comparable (Table 3). C_{peak} were approximately twofold higher in HCV-infected patients at doses ≥200 mg once-daily compared to healthy subjects. C_{peak} on day 3 ranged from 6.5 to 274 ng/ml for the IDX320 once-daily dosing regimen, while E_{C_{peak}} values were 2.7/4.2 ng/ml in the genotype 1a replicon and 0.4/1.2 ng/ml in the genotype 1b replicon. Urine excretion of IDX320 was negligible (<0.01% of administered doses).

Antiviral activity
Antiviral activity of IDX320 was first observed in two genotype 1a HCV-infected patients, who received a single dose of 200 mg. Maximal HCV RNA reductions were 1.9 log_{10} IU/ml at 12 h in the treatment-naive patient and 2.8 log_{10} IU/ml at 36 h in the treatment-experienced patient after a single dose. Mean changes in HCV RNA for the 38 treatment-naive patients who received IDX320 monotherapy for 3 days are displayed in Figure 2A and Table 4. IL28B genotype status appeared to have no effect on antiviral activity through day 3. None of the patients experienced virological breakthrough (defined as a 1 log_{10} increase of HCV RNA above nadir) during IDX320 treatment. No patient achieved undetectable levels of HCV RNA by day 3. Individual HCV RNA curves are displayed in Figure 2B. A total of 26 (68%) patients initiated PEG-IFN/RBV after 3 days IDX320 monotherapy. Treatment response at day 28 in those patients who received PEG-IFN/RBV during the follow-up period are displayed in Figure 2B.
Safety and tolerability
All enrolled healthy subjects and HCV-infected patients completed the study. There were no serious adverse events. A summary of the reported clinical adverse events in chronic hepatitis C-infected patients is listed in Table 5. Adverse events during the IDX320 treatment period were rare, mild to moderate in intensity and without any discernable patterns between the IDX320 treatment groups and placebo groups. With the exception of one patient (200 mg once-daily group) with a single grade 3 serum calcium decrease among otherwise normal calcium values, and another patient (200 mg twice-daily group) who had an asymptomatic increase in lipase from grade 2 at screening to grade 3 on day 2 (pancreatic amylase remained normal), laboratory abnormalities during the IDX320 treatment period were all grade 2 or below, the majority being grade 1. With the exception of bilirubin, there were no patterns in graded laboratory abnormalities noted between the IDX320 and placebo groups. Although comparable to placebo in the IDX320 once-daily treatment groups, there were more grade 1/2 total serum bilirubin elevations in the 200 mg twice-daily treatment group (Table 5). The elevations were primarily of direct bilirubin. Patients with bilirubin increases were asymptomatic and did not have associated increases of ALT, aspartate aminotransferase (AST) or alkaline phosphatase. Serum bilirubin returned to baseline levels within 4 days of the last dose of IDX320. Adverse events and laboratory abnormalities after the IDX320 treatment period were consistent with PEG-IFN/RBV events and laboratory abnormalities after the IDX320 (plus the D168G/D) showed conferred resistance in vitro. A summary of the reported clinical adverse events is listed in Table 5. Adverse events during the IDX320 treatment appeared to be selected by IDX320.

Mutational analysis
Previous in vitro work with IDX320 selection experiments and evaluation of site-directed mutants identified the D168 locus as the primary site of resistance to IDX320, with several other sites (Q80, R155 and A156) conferring mild to moderate resistance to IDX320 when mutated [15]. Population sequences from the entire NS3/NS4A region were analysed before and after treatment. Random, low frequency substitutions were observed throughout the NS3/NS4A region, but several post-treatment changes were observed at loci known to confer in vitro resistance to IDX320, specifically loci Q80, A156 and D168.

Neither of the two patients enrolled in the single-dose part of this study showed a change at any of the resistance loci, nor did any of the patients enrolled in the three-day dosing portion of the study who received IDX320 show any resistance variants at baseline. Two genotype 1a patients had a baseline R80 polymorphism. Both patients were assigned to receive placebo and were therefore not included in this analysis.

Overall, 6 of 30 genotype 1b patients receiving IDX320 for 3 days developed mutations at day 3 at three loci that are associated with in vitro resistance to IDX320 (Table 6). Two patients had Q80R, one patient had A156T, two patients had D168V and one patient had a mixed population of G/D at position 168. No changes at amino acid R155 were observed. D168G was not observed in the in vitro selection experiments; however, because the D168 locus was observed to mutate in vitro in response to IDX320 treatment, the D168G/D patient was included in the resistance summary.

All 6 patients whose virus developed mutations that conferred resistance in vitro (plus the D168G/D) showed substantial declines in viral load at day 3 relative to baseline (Table 6). In 3 patients, whose viral loads increased after the completion of IDX320 dosing, the observed day 3 mutations returned to wild type at day 6. No other changes in NS3 sequences from baseline to the end of treatment appeared to be selected by IDX320.

Discussion
This was an ascending single- and multiple-dose study in healthy volunteers and hepatitis C patients conducted in sequential steps. The first two parts of the

<table>
<thead>
<tr>
<th>Table 3. Pharmacokinetic parameters of IDX320 after 3 days dosing in healthy volunteers and in hepatitis C patients</th>
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</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Healthy subjects</td>
</tr>
<tr>
<td>400 mg once daily</td>
</tr>
<tr>
<td>Chronic hepatitis C patients</td>
</tr>
<tr>
<td>50 mg once daily</td>
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<tr>
<td>100 mg once daily</td>
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<tr>
<td>200 mg once daily</td>
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<tr>
<td>400 mg once daily</td>
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<tr>
<td>200 mg twice daily</td>
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</table>

Values are reported as means ±SD, except for time to mean peak concentration (T<sub>max</sub>), where medians (range) are reported. AUC<sub>24h</sub>, area under the curve at 24 h; C<sub>trough</sub>, trough concentration; T<sub>1/2</sub>, terminal half-life.
The primary objective of this Phase Ib study was to assess safety, tolerability and antiviral activity of 3 days of IDX320 or placebo monotherapy, either once daily (part C) or twice daily (part D), before extended follow-on therapy with PEG-IFN and RBV was offered.

 IDX320 treatment resulted in rapid reductions of HCV RNA. (A) Mean changes of HCV RNA levels from baseline for all treatment groups receiving IDX320 or placebo for 3 days. (B) Individual HCV RNA decline is depicted for all dose cohorts. None of the patients experienced virological breakthrough (defined as a 1 log₁₀ increase of HCV RNA above nadir) during treatment with IDX320.
HCV RNA reduction at day 3

×

bilirubin values,

Adverse event

640

is comparable with the mean HCV RNA decline of their respective IDX320 dose cohorts. NS3 mutations were observed in all IDX320 dose cohorts in six patients by population sequencing. The individual HCV RNA declines of the six patients with NS3 mutations

406

3

327

318

317

406

313

324

Individual maximum direct bilirubin values, ×ULN

–

2.8

2.5, ≤1a

≤1

5.2, 3.8, ≤1, ≤1a

2.1, ≤1a

For patients with grade 1/2 total bilirubin elevations from baseline values. aEach value represents an individual patient. ULN, upper limit of normal.

Table 6. Mutations observed at NS3 amino acid positions 80, 156 and 168 and the mean HCV RNA decline from baseline after 3 days of IDX320 dosing

<table>
<thead>
<tr>
<th>Patient</th>
<th>NS3 mutations</th>
<th>Individual HCV RNA decline, log₁₀ IU/mla</th>
<th>Cohort mean HCV RNA decline, log₁₀ IU/mla</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 3</td>
<td>Day 6</td>
</tr>
<tr>
<td>318</td>
<td>WT</td>
<td>Q80R</td>
<td>WT</td>
</tr>
<tr>
<td>327</td>
<td>WT</td>
<td>A156T</td>
<td>WT</td>
</tr>
<tr>
<td>317</td>
<td>WT</td>
<td>D168G/D</td>
<td>WT</td>
</tr>
<tr>
<td>406</td>
<td>WT</td>
<td>D168V</td>
<td>NAa</td>
</tr>
<tr>
<td>313</td>
<td>WT</td>
<td>Q80R</td>
<td>NAa</td>
</tr>
<tr>
<td>324</td>
<td>WT</td>
<td>D168V</td>
<td>NAa</td>
</tr>
</tbody>
</table>

NS3 mutations were observed in all IDX320 dose cohorts in six patients by population sequencing. The individual HCV RNA declines of the six patients with NS3 mutations is comparable with the mean HCV RNA decline of their respective IDX320 dose cohorts. aAt day 3. bNot available (NA) because viral load was <1,000 IU/ml. WT, wild type.

IDX320. There were no serious adverse events or premature discontinuations. There were no discernable patterns in any clinical or laboratory safety parameters in Parts A and B. Headache was the most common reported adverse event in the study, without any clear relationship to IDX320 dose. There were asymptomatic grade 1/2 elevations of direct bilirubin, without associated increases in ALT, AST or alkaline phosphatase, in HCV-infected patients who received IDX320 200 mg twice daily for 3 days. These observations were consistent with the in vitro inhibition of MRP2 and BSEP by IDX320. IDX320 is a potent inhibitor of these human
hepatic efflux transporters with IC_{50}<0.5–5 uM. Adverse events and laboratory abnormalities during the follow-up period in HCV-infected patients (in Parts C and D) were consistent with PEG-IFN/RBV dosing, which began after day 3 in the majority (68%) of the patients. Bilirubin elevations have been observed with other HCV protease inhibitors in development, such as TMC435 (total, direct and indirect), BI201335 (indirect) and GS-9256 (indirect) [21–23]. Alisporivir, a cyclophilin inhibitor, also caused elevations in total and direct bilirubin [24].

IDX320 demonstrated potent dose-related antiviral activity in genotype 1 HCV-infected patients. There was a pharmacokinetic/pharmacodynamic relationship between the day 3 viral response and the C_{trough} of IDX320 following the third dose, such that higher C_{trough} were associated with better antiviral responses (Additional file 2). Antiviral activity beyond the EC_{50} and approximately 300- to 1,000-fold above the genotype 1a EC_{50} after repeat daily dosing of IDX320 was observed during the 3-day dosing portion of the IDX320 dosing period for all dose levels. The mean C_{trough} of IDX320 achieved in the 400 mg once-daily dosing group was 228 ng/ml, representing 685× the EC_{90} value and 228× the EC_{50} value determined in 20 healthy volunteers.

In conclusion, single and multiple doses for 3 days of IDX320 in healthy volunteers and HCV-infected patients were safe and well tolerated. Oral once-daily administration of IDX320 for 3 days resulted in a rapid HCV RNA decline in all patients. Although the results of this study demonstrated the clinical potential of IDX320, further development of IDX320 was stopped when three serious adverse events of increased liver enzymes occurred during a drug–drug interaction study of IDX320 and IDX184 (nucleotide HCV polymerase inhibitor) in 20 healthy volunteers.

Acknowledgements

The authors wish to thank all the healthy volunteers and HCV-infected patients who generously agreed to participate in this clinical study. We also acknowledge the contribution of MW Peters (trial nurse, Academic Medical Center, Amsterdam, the Netherlands).

Disclosure statement

This study was sponsored by Idenix Pharmaceuticals, Inc. HR serves as advisor for Roche Molecular Diagnostics, Anadys, Merck/Schering–Plough, Astex, Tibotec/Janssen Cilag and PRA International, and receives grant/research support from Merck/Schering-Plough, Anadys, Santaris, Roche, Idenix and PRA International. X-JZ, M-FT, JM, JC, KP, JFM, JZS-B and DM...
are employees of Idenix Pharmaceuticals, Inc. All other authors declare no competing interests.

Additional files

Additional file 1: A figure illustrating mean plasma concentration-time profile during 3 days IDX320 administration and 4 days post-dosing in hepatitis C patients can be found at http://www.intmedpress.com/uploads/documents/AVT-11-OA-2205_de_Bruijne_Add_file1.pdf

Additional file 2: A figure illustrating the relationship between HCV RNA change at day 3 and IDX320 plasma C\textsubscript{trough} can be found at http://www.intmedpress.com/uploads/documents/AVT-11-OA-2205_de_Bruijne_Add_file2.pdf

References