Oral IDN-6556, an Antiapoptotic Caspase Inhibitor, May Lower Aminotransferase Activity in Patients with Chronic Hepatitis C

Paul J. Pockros,[1] Eugene R. Schiff,[2] Mitchell L. Shiffman,[3] John G. McHutchison,[4] Robert G. Gish,[5] Nezam H. Afdhal,[6] Manana Makhviladze,[7] Mira Huyghe,[8] David Hecht,[8] Tilman Oltersdorf,[8] and David A. Shapiro[8]

Increased rates of apoptosis (programmed cell death) have been demonstrated in many hepatic diseases including chronic hepatitis C. IDN-6556 is a potent inhibitor of caspases, the proteases that execute apoptosis. In a prior phase 1 study, IDN-6556 lowered aminotransferase activity in a small number of patients with liver impairment. The purpose of this study was to further explore the effect of IDN-6556 in patients with liver disease in a multicenter, double-blind, placebo-controlled, dose-ranging study with a 14-day dosing period. A total of 105 patients were enrolled in the study; 79 received active drug; 80 patients had chronic hepatitis C and 25 had other liver diseases including nonalcoholic steatohepatitis (NASH), hepatitis B, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). IDN-6556 doses ranged from 5 mg to 400 mg daily, given from 1 to 3 times per day. In the HCV patients, all doses of IDN-6556 significantly lowered ALT and AST ($P = 0.0041$ to $P < 0.0001$ for various dosing groups in Wilcoxon tests comparing IDN-6556 to placebo), with the exception of the lowest dose. Declines in aminotransferase activity were also seen in patients with NASH but effects were not apparent in the small number of other liver diseases. Adverse experiences were not different between IDN-6556 and placebo. There were no clinically meaningful changes in other laboratory parameters. In particular, mean HCV RNA levels did not show significant changes. *Conclusion:* Oral IDN-6556, given for 14 days, significantly lowered aminotransferase activity in HCV patients and appeared to be well tolerated. Longer studies to assess potential effects of IDN-6556 on liver inflammation and fibrosis are merited. (HEPATOLOGY **2007;46:324-329.**)

Programmed cell death or apoptosis is a tightly controlled process of cellular suicide that occurs during normal development, normal tissue turnover, and in numerous diseases.[1] Caspases are proteolytic enzymes that cleave a series of cellular substrates during the execution phase of apoptosis. Caspases are activated from their inactive zymogen forms (procaspases) when a cell is triggered to undergo apoptosis. IDN-6556 is a novel broad-

Abbreviations: BID, twice daily; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; QD, once daily; TID, three times daily.

From the [1]Division of Gastroenterology and Hepatology, Scripps Clinic, La Jolla, CA; [2]Center for Liver Diseases, University of Miami, Miami, FL; [3]Hepatology Section, Virginia Commonwealth University Medical Center, Richmond, VA; [4]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC; [5]Hepatology and Gastroenterology Research Center, California Pacific Medical Center, San Francisco, CA; [6]Liver Center, Beth Israel Deaconess Medical Center, Boston, MA; [7]State Medical Academy, T'bilisi, Republic of Georgia; [8]Idun Pharmaceuticals Inc., San Diego, CA.

Received November 20, 2006; accepted January 22, 2007.

This clinical study was sponsored by Idun Pharmaceuticals, Inc., now owned by Pfizer, Inc.

Address reprint requests to: Paul J Pockros, M.D., Division of Gastroenterology / Hepatology, Scripps Clinic, 10666 N. Torrey Pines Road, La Jolla, CA. 92037. e-mail: pockros.paul@scrippshealth.org; fax: 858-554-8065.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.21664

Potential conflict of interest: Dr. Shapiro is an employee and owns stock in Idun Pharmaceuticals. He is also a consultant for Pfizer, Inc. Dr. Oltersdorf is an employee and owns stock in Idun Pharmaceuticals. Dr. Pockros is a consultant for, advises, and received grants from Idun Pharmaceuticals. Dr. Schiff is a consultant for, received grants, and is on the speakers' bureau of Gilead, Ortho-Biotech, and Schering-Plough. He is also a consultant and received grants from Abbott, Bristol-Myers Squibb, Cadence Pharmaceuticals, GlaxoSmithKline, Idenix, Prometheus, Roche Molecular, and SciClone Pharmaceuticals. He is a consultant for Achillion Pharmaceutical, Cadence Pharmaceuticals, GlobeImmune, Inc., Pharmasset, Inc., Pfizer, Salix Pharmaceuticals, Inc., and Novartis/Idenix. Dr. Shiffman is a consultant and received grants from Idun Pharmaceuticals and Pfizer. Dr. McHutchison received grants from Idun Pharmaceuticals and Pfizer. Dr. Gish received grants, is a consultant, and is on the speakers' bureau of Bristol Myers Squibb, Eximias, F. Hoffmann-LaRoche Ltd., Gilead Sciences, InterMune Pharmaceuticals, Ortho-Biotech, Schering-Plough Corp., SciClone Pharmaceuticals, Valeant Pharmaceuticals, PowderMed, and GlobeImmune. He also received grants from Pfizer, Idun Pharmaceuticals, and Idenix/Novartis. He is also a consultant and is on the speakers' bureau for Bayer AG and GlaxoSmithKline. He is a consultant for Amgen Inc., Anadys Pharmaceuticals, Inc., Chiron Corp., Corixa Corp., Human Genome Sciences, Metabasis Therapeutics, United Therapeutics, XTL Biopharmaceuticals, Zymogenetics, Inc., Pharmaseet, Idenix, Hepahope, Nucleonics, and Innogenetics. He is on the speakers' bureau of Salix. Dr. Afdhal advises and received grants from Idun Pharmaceuticals.

spectrum caspase inhibitor with activity against all tested human caspases. IDN-6556 is a specific and irreversible caspase inhibitor that shows no inhibition of other classes of proteases or other enzymes or receptors.[2] IDN-6556 has been shown to have activity in animal models of liver disease in which apoptosis is thought to contribute to the pathogenesis. For instance, apoptosis has been described in a model of liver fibrosis occurring after ligation of the mouse bile duct. In this model, application of IDN-6556 suppresses apoptosis and inflammation and prevents liver fibrosis.[3] In a rat model of ischemia/reperfusion injury during liver transplantation, IDN-6556 lowered aminotransferase activity and improved liver function.[4]

In human hepatic disease the presence of increased levels of apoptotic cells in the liver has been demonstrated in hepatitis C,[5,6] hepatitis B,[7] nonalcoholic steatohepatitis (NASH),[8] acute alcoholic hepatitis,[9-12] primary biliary cirrhosis (PBC), autoimmune hepatitis,[13] and after liver transplantation.[14,15] Furthermore, in hepatitis C the number of apoptotic cells present in liver biopsies have been shown to correlate with the grade of inflammation.[5]

IDN-6556 was tested earlier in a phase 1 study in human volunteers by intravenous administration.[16] In the phase 1 study, local phlebitis in the vein used for intravenous administration occurred and was a dose-limiting toxicity. Otherwise the drug was generally well tolerated. A group of 16 volunteers with elevated aminotransferase activity were also studied; including patients with hepatitis C, probable nonalcoholic fatty liver disease, alcoholic liver disease, and others without a known diagnosis. Administration of IDN-6556 led to a significant decline of ALT and AST levels in this group.[16]

The purpose of the study reported here was to explore the safety and efficacy of IDN-6556 given by oral administration for the first time in patients with liver disease. In particular, the study focused on effects on aminotransferase activity and HCV-RNA levels in a large subgroup of patients with hepatitis C.

Patients and Methods

Study Design

We enrolled 105 patients in a multicenter, double-blind, placebo-controlled, dose-ranging study with 14 days of IDN-6556 administered orally. We designed this trial to explore the effects of a range of doses and dosing intervals, but we did not design it as a formal, parallel group dose response study. We assigned 8 patients to each dosing group, with 6 patients receiving active drug and 2 patients receiving placebo. We studied a total of 14 dosing groups. For the hepatitis C patients, we tested a total of 9 different doses [5 mg, 25 mg, 100 mg, and 200 mg, given once daily (QD) and twice daily (BID), and 5 mg given three times daily (TID)]. For the patients with hepatitis B, NASH, PBC, and primary sclerosing cholangitis (PSC), we tested a single dosage (100 mg BID). The protocol was approved by the Institutional Review Boards of all participating centers. All enrolled patients agreed to participation by written informed consent. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki including subsequent amendments and clarifications through 2001 (http://www.wma.net/e/ethicsunit/helsinki.htm).

Patient Selection and Procedures

We designed inclusion and exclusion criteria to allow patients with compensated liver disease into the study. We accepted patients into the study if they had ALT or AST elevations between 1.5 and 10 times the upper limit of the normal range and fibrosis stages F0 through F3 on a liver biopsy performed within 36 months of enrollment. We excluded patients with cirrhosis on biopsy or decompensated liver disease. A total of 80 patients had a diagnosis of hepatitis C and 90% of these were infected with HCV genotype 1. We accepted HCV patients for enrollment if they had HCV RNA (PCR) $>10^5$ IU/mL and no other cause for liver disease based on their liver biopsy. We defined patients as having NASH if their liver biopsy demonstrated at least 1+ steatosis and ballooning hepatocytes with inflammation and/or fibrosis. We defined patients as having PBC if they had a positive antimitochondrial antibody test, characteristic changes on liver biopsy, and an elevation of serum alkaline phosphatase. Patients with PSC had characteristic features on cholangiogram and a negative serum antimitochondrial antibody test. We defined patients as having hepatitis B by a positive serum test for hepatitis B surface antigen, a titer of HBV DNA (PCR)$> 10^4$ copies/mL by the Roche COBAS TaqMan HBV DNA assay (lower level of detection <50 copies/mL), and no other cause for liver disease. Data for pretreatment HBV DNA and serology were unavailable for some patients, making it unclear whether they had acute or chronic disease. We discarded viral responses in these patients from our final analysis because of this uncertainty.

The baseline characteristics of the patients are summarized in Table 1. There were no significant differences in gender, age, or viral genotype for the treated groups versus the placebo groups. We saw the patients at screening and baseline visits before dosing and we saw them frequently during the treatment and posttreatment follow-up periods.

Table 1. Baseline Characteristics of 105 Patients with Liver Disease

Characteristic	Value (%)
Sex	
Female	n = 41 (39)
Male	n = 64 (61)
Age (years)	47.3
Diagnosis	
Hepatitis C	n = 80 (76)
Hepatitis B	n = 13 (12)
NASH	n = 5 (5)
PBC or PSC	n = 7 (7)
If HCV-positive	
Genotype	
1	72 (90)
2	5 (6)
3	3 (4)

Dose Selection and Treatment Schedule

The study covered an 80-fold dose-range, from 5 mg to 400 mg daily, administered orally, QD, BID, or TID. Consistent with the exploratory nature of the study, we unblinded each dosing group after the completion of the 14-day dosing period prior to the decision for dose-adjustment for the following dosing group. Although we designed the study to accept patients with all liver diseases, all but 1 of the first 40 patients had a diagnosis of HCV. We continued dose-ranging in groups with HCV patients; 2 groups of patients received 5 mg BID, and overall, we exposed patients to doses ranging from 5 mg to 400 mg daily. We opened diagnosis-specific dosing groups during the further course of the study to evaluate different disease populations more formally. Smaller numbers of patients with HBV, NASH, PBC, or PSC all received a fixed dose of 100 mg BID.

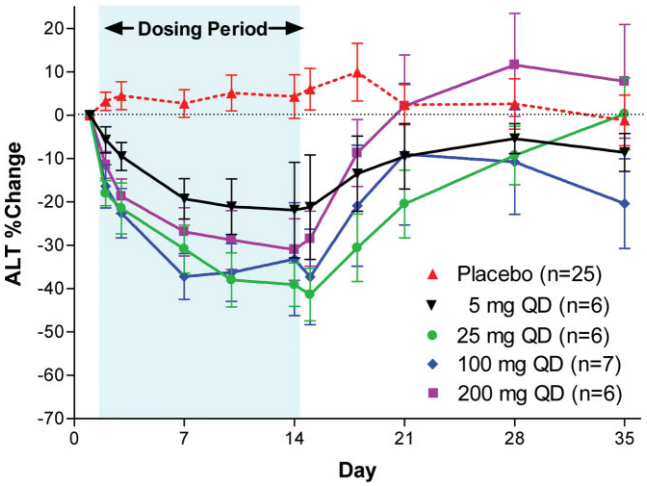

Fig. 1. ALT: percent change from baseline, QD dosing, means ± SEM are shown.

We conducted compliance for drug dosing (via pill counts) at all visits. Overall compliance was excellent (≥98%) in each dosing group.

Monitoring

We performed blood and serum analyses at screening and baseline visits and on days 1, 2, 3, 7, 10, and 14 during the treatment period, and on days 15, 18, 21, 28, and 35 during an observation and follow-up period. In patients with hepatitis C or B, we obtained viral RNA or DNA levels at baseline and on days 7, 14, 21, and 35. In females with reproductive potential, we performed a pregnancy test at the screening visit. We included physical exams at the screening visit and on days 1, 7, 14, 21, 28, and 35. We monitored and assessed adverse events at every visit.

Statistical Analysis

We examined absolute and relative peak changes in aminotransferase activity during the dosing period by Wilcoxon test for pairwise comparison and by one-way analyses of variance. We used the mean of screening, baseline, and day 1 values immediately before the first dose of the drug as the baseline for calculation of relative changes. Peak changes used for the calculations all occurred on days 14 or 15. The significance level used was 0.05 for all tests.

Results

IDN-6556 lowers aminotransferase activity in HCV patients. All doses of 5 mg BID and above led to a statistically significant decrease of aminotransferase levels. In the QD dosing groups, the mean ALT decrease at day 14 or 15 ranged from 31% (200 mg QD) to 41% (25 mg QD). In the BID and TID dosing groups the ALT decrease ranged from 39% (50 mg BID) to 56% (100 mg BID) (Figs. 1 and 2). AST responses were of a similar

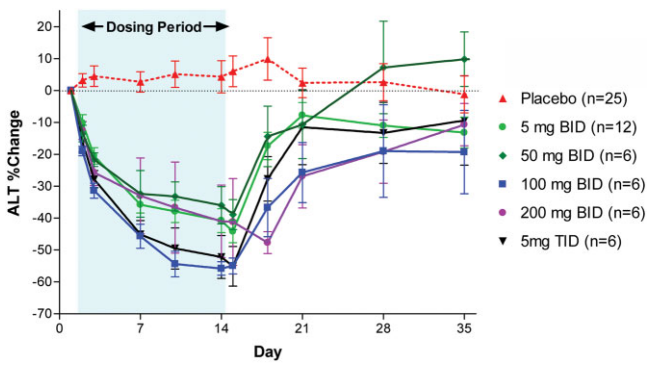

Fig. 2. ALT: percent change from baseline, BID and TID dosing, means ± SEM are shown.

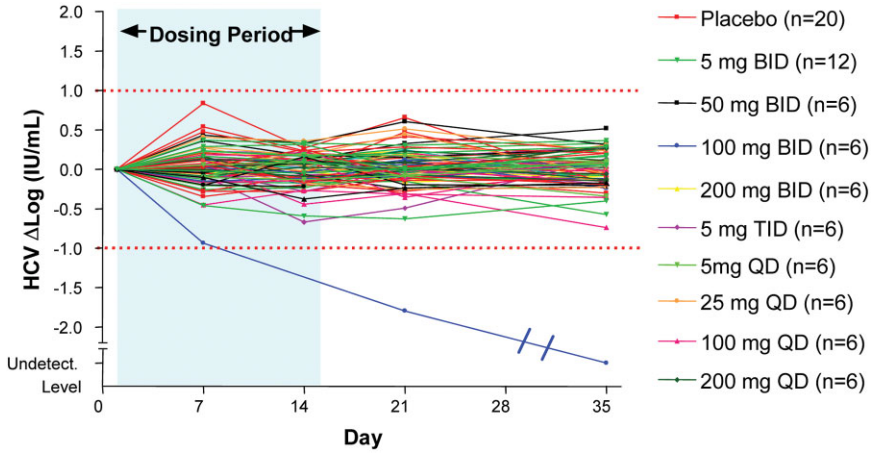

Fig. 3. Change in HCV-RNA levels in 80 patients with HCV

magnitude (data not shown). The lowest dose of 5 mg QD showed a mean ALT reduction of 22% ($P < 0.05$) and a corresponding AST reduction of 15% (not significant). Wilcoxon tests for pairwise comparisons of the relative peak ALT changes showed that all HCV treatment groups above 5 mg QD were significantly different from placebo (P values ranging from 0.0041 to <0.0001). BID and TID dosing was apparently more efficacious than QD dosing. Otherwise there was no apparent dose-response above the 5 mg QD dose. All the patients with HCV showed an improvement in ALT or AST activities. However, a minority of the patients normalized their ALT or AST values; this approached 50% in the BID and TID dosing regimens, but was only 20% for the QD dosing.

In the 26 placebo patients the mean aminotransferase value remained essentially unchanged (ALT at day 14 was increased by 4.3; not significant).

HCV-RNA Does Not Increase During Treatment with IDN-6556

Figure 3 demonstrates that HCV-RNA levels remained stable within 1 log unit during the study with the exception of 1 patient who received 100 mg BID. This patient's viral RNA levels declined below the detection limit during the observation and follow-up period. However, during further observation this patient's HCV-RNA returned to prestudy levels. Under a protocol amendment, we re-treated the patient with IDN-6556 for a month. During this second treatment period HCV levels remained unchanged whereas aminotransferase activity declined as during the previous treatment period.

Decreased Aminotransferase Activity in Patients with Other Liver Diseases

We studied patients with diagnoses other than chronic hepatitis C who received IDN-6556 in various disease specific groups; all received 100 mg BID. These groups included: (1) NASH (n = 5); (2) chronic cholestatic disorders [PSC (n = 2), PBC (n = 3), and secondary biliary cirrhosis (n = 2)]; and (3) chronic hepatitis B (n = 13). The hepatitis B patients included a group of 9 patients with untreated hepatitis B whom we recruited in the Republic of Georgia and a subsequent group of 4 patients we recruited at U.S. centers. Due to the small patient numbers, we presented no formal statistical analysis. In patients with NASH or HBV, mean ALT decreased by 59% and 47% from baseline, respectively, similar to patients with HCV, although there was more variability in both the placebo and drug-treated patients with HBV than with HCV (Fig. 4).

Patients with chronic cholestatic disorders showed less-clear responses. One PSC patient experienced a flare in aminotransferase activity, which their investigator ascribed to preexisting cholangitis. The second PSC patient showed a 54% decline from day 1 ALT. The 3 PBC patients showed variable declines of 10%, 26%, and 53%. However, there were no meaningful changes in alkaline phosphates levels in these patients.

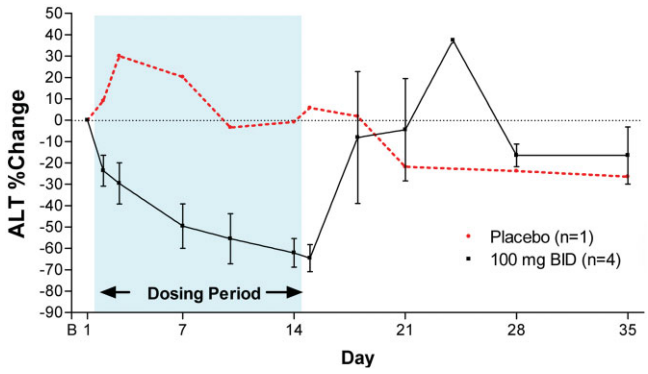

Fig. 4. ALT: percent change from baseline, 100 mg BID dosing, means ± SEM in 4 patients with NASH are shown.

Table 2. Summary of Adverse Events Across All Dose Groups: Events with Incidence >1 in Treatment Groups

Adverse Event (MedDRA Preferred Term)	IDN-6556 (n = 79)		Placebo (n = 26)	
	n	%	n	%
Patients with any event	39	49	14	54
Abdominal pain (upper)	6	8	0	0
Dyspepsia	6	8	0	0
Fatigue	6	8	3	12
Dizziness	6	8	0	0
Headache	6	8	1	4
Nasopharyngitis	5	6	1	4
Diarrhea	4	5	4	15
Nausea	4	5	4	15
Arthralgia	3	4	0	0
Abdominal pain	2	3	2	8
Abdominal distension	2	3	2	8
Dry mouth	2	3	1	4
Flatulence	2	3	0	0
Pain	2	3	1	4
Dysgeusia	2	3	0	0
Pharyngolaryngeal pain	2	3	2	8
Pruritus	2	3	1	4

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

Safety

Adverse events were generally mild and brief (Table 2). Overall, there were no significant differences between placebo and drug-treated patients. Patients on active treatment reported a higher frequency of "upper abdominal pain," whereas the placebo patients reported a higher frequency of "abdominal pain" and "abdominal distension." There was no clear dose relationship of adverse events across the 80-fold range of doses studied (data not shown). In the previous phase 1 study, 3 patients had temporary increases of aminotransferase activity after discontinuation of treatment.[16] In this study, we defined aminotransferase "overshoot" as a >50% increase above baseline after discontinuation of treatment. One patient with NASH experienced such an overshoot, with an ALT value of 372 U/L at day 18 compared to 178 U/L at day 1. Upon further observation, ALT returned to 239 U/L at day 35. In addition, the PSC patient mentioned above with a flare of preexisting cholangitis during IDN-6556 therapy also met the criteria for overshoot after the end of treatment. No other patient met the criteria for overshoot during the follow-up period after discontinuation of IDN-6556. There was no evidence for the development of hepatocellular carcinoma in any of the 105 patients studied during the treatment and follow-up periods.

Discussion

This study demonstrates that IDN-6556 can reduce aminotransferase activity rapidly and significantly in patients with chronic HCV infection during a 2-week dosing period without apparent drug-related adverse experiences. We observed a similar trend in the patients with HBV and NASH, although we did not perform statistical analysis in these groups. The changes in hepatic enzymes in the small group of patients with chronic cholestatic disease were unclear. We presume that the effect of IDN-6556 on aminotransferase activity is due to its antiapoptotic effect, preventing the death of hepatocytes and thus preventing the release of aminotransferase activity, although this point remains unproven. In chronic liver diseases, apoptosis may occur as a result of death receptor signaling, in particular activation of the Fas pathway.[6,17,18] IDN-6556 can effectively block Fas-induced apoptosis in vitro and in animal models.[2,3] Thus it is possible that suppression of aminotransferase levels is, in part, due to a decrease of Fas-induced death of hepatocytes. The efficient reduction of aminotransferase activity caused by IDN-6556 raises the question whether IDN-6556 can affect the natural progression of chronic liver disease. Other agents known to lower aminotransferase activity such as silymarin and ribavirin (when used alone) do not have significant effects on disease progression.[19,20] However, these agents lower aminotransferase activity much more slowly and presumably by different mechanisms. Longer studies with IDN-6556 are needed to determine whether it can affect endpoints such as serum markers of apoptosis, inflammation, and fibrosis on liver biopsy and ultimately clinical outcomes of chronic liver disease.

In this 14-day study, we observed no apparent drug-related adverse events. However, the mechanism of action of IDN-6556 as an antiapoptotic caspase inhibitor has raised theoretical safety concerns in the past. In particular, we postulated that inhibition of apoptosis in patients with virus infections might increase the viral load by keeping virus-producing cells alive. In this study no clinically meaningful increase in either the HCV or HBV viral load was apparent.

Another theoretical area of concern was the possibility that inhibition of apoptosis could lead to the accumulation of blood cells in tissues with rapid cell turnover. In this study no drug-effect on accumulation of blood cells was apparent. The apparent lack of mechanism-based side effects in this study may be due to the redundancy in apoptotic signaling pathways. Caspase inhibitors like IDN-6556 can efficiently block death-receptor-mediated apoptosis in the "extrinsic" death pathway.[1] However, in other models, caspase inhibition can only delay but not prevent cell death mediated through mitochondrial dysfunction and the "intrinsic" death pathway.[1] Caspase inhibitors cannot block any caspase-independent pathways.

A third potential area of concern was the occurrence of an aminotransferase flare or overshoot after withdrawal of IDN-6656. One patient in this study and 3 patients in a previous study experienced overshoot of aminotransferase activity after discontinuation of the drug.[16] In all cases, aminotransferase activity spontaneously returned toward the baseline on further observation. To prevent or suppress such overshoot of aminotransferase activity, in future studies we should consider tapering regimens instead of abrupt drug withdrawal.

A fourth and final area of concern is the risk of development of cancer with the use of a potent antiapoptotic caspase inhibitor. Because of this concern, we excluded patients from enrollment in this study if they had cirrhosis or elevation of alpha-fetoprotein levels, and we limited the duration of treatment to a 14-day dosing period. Future studies with a longer duration of treatment will require careful and long-term follow-up of patients for the development of hepatocellular carcinoma, especially those with cirrhosis due to HCV or HBV.

We did not design this study as a formal dose-response study, and therefore limited conclusions about differences between doses can be made. However, we evaluated an unusually wide range of doses in this study (80-fold or 1.4 log), and although there was no clear dose-response relationship across the various doses (except for 5 mg given QD that appeared to be less efficacious), QD dosing was less efficacious than more frequent dosing. However, we did not identify a dose that had no efficacy, so the minimally effective dosage is unknown. A subsequent study is evaluating the dose-response relationship of BID dosing in larger numbers of patients and to determine the minimally effective dosage. In conclusion, longer and larger studies with IDN-6556 are merited to further assess the drug's safety and efficacy with chronic administration.

Acknowledgment: We thank all the study coordinators involved in the study for their dedication and hard work, in particular Clarissa Navarro, Lee Goodman, Heather Raley, and Denice Shelton. We also thank Martin Krauss and his colleagues at FGK Clinical Research GmbH, Planegg-Martinsried, Germany for the statistical analysis and data management. Patients in the Republic of Georgia were recruited through Evidence Clinical and Pharmaceutical Research, Los Altos, CA and T'bilisi, and we thank Zaza Chapichadze, MD, PhD, Tamara Tchelidze, MD, and Pyotr Platonov, MD, PhD for their efforts in organizing the research there).

References

1. Danial NN, Korsmeyer SJ. Cell death: critical control points. Cell 2004; 116:205-219.
2. Hoglen NC, Chen LS, Fisher CD, Hirakawa BP, Groessl T, Contreras PC. Characterization of IDN-6556 (3-[2-(2-tert-butyl-phenylaminooxalyl)-amino]-propionylamino]-4-oxo-5-(2,3,5,6-tetrafluoro-phenoxy)-pentanoic acid): a liver-targeted caspase inhibitor. J Pharmacol Exp Ther 2004;309:634-640.
3. Canbay A, Feldstein A, Baskin-Bey E, Bronk SF, Gores GJ. The caspase inhibitor IDN-6556 attenuates hepatic injury and fibrosis in the bile duct ligated mouse. J Pharmacol Exp Ther 2004;308:1191-1196.
4. Natori S, Higuchi H, Contreras P, Gores GJ. The caspase inhibitor IDN-6556 prevents caspase activation and apoptosis in sinusoidal endothelial cells during liver preservation injury. Liver Transpl 2003;9:278-284.
5. Bantel H, Lugering A, Poremba C, Lugering N, Held J, Domschke W, et al. Caspase activation correlates with the degree of inflammatory liver injury in chronic hepatitis C virus infection. HEPATOLOGY 2001;34:758-767.
6. Pianko S, Patella S, Ostapowicz G, Desmond P, Sievert W. Fas-mediated hepatocyte apoptosis is increased by hepatitis C virus infection and alcohol consumption, and may be associated with hepatic fibrosis: mechanisms of liver cell injury in chronic hepatitis C virus infection. J Viral Hepat 2001; 8:406-413.
7. Galle PR, Krammer PH. CD95-induced apoptosis in human liver disease. Semin Liver Dis 1998;18:141-151.
8. Feldstein AE, Canbay A, Angulo P, Taniai M, Burgart LJ, Lindor KD, et al. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. Gastroenterology 2003;125:437-443.
9. Day CP. Apoptosis in alcoholic hepatitis: a novel therapeutic target? J Hepatol 2001;34:330-333.
10. Natori S, Rust C, Stadheim LM, Srinivasan A, Burgart LJ, Gores GJ. Hepatocyte apoptosis is a pathologic feature of human alcoholic hepatitis. J Hepatol 2001;34:248-253.
11. Pianko S, Patella S, Sievert W. Alcohol consumption induces hepatocyte apoptosis in patients with chronic hepatitis C infection. J Gastroenterol Hepatol 2000;15:798-805.
12. Ziol M, Tepper M, Lohez M, Arcangeli G, Ganne N, Christidis C, et al. Clinical and biological relevance of hepatocyte apoptosis in alcoholic hepatitis. J Hepatol 2001;34:254-260.
13. Fox CK, Furtwaengler A, Nepomuceno RR, Martinez OM, Krams SM. Apoptotic pathways in primary biliary cirrhosis and autoimmune hepatitis. Liver 2001;21:272-279.
14. Natori S, Selzner M, Valentino KL, Fritz LC, Srinivasan A, Clavien PA, et al. Apoptosis of sinusoidal endothelial cells occurs during liver preservation injury by a caspase-dependent mechanism. Transplantation 1999;68:89-96.
15. Schnurr C, Glatzel U, Tolba R, Hirner A, Minor T. Fas receptor is upregulated in livers from non-heart-beating donors. Eur Surg Res 2001;33: 327-333.
16. Valentino KL, Gutierrez M, Sanchez R, Winship MJ, Shapiro DA. First clinical trial of a novel caspase inhibitor: anti-apoptotic caspase inhibitor, IDN-6556, improves liver enzymes. Int J Clin Pharmacol Ther 2003;41: 441-449.
17. Faouzi S, Burckhardt BE, Hanson JC, Campe CB, Schrum LW, Rippe RA, et al. Anti-Fas induces hepatic chemokines and promotes inflammation by an NF-kappa B-independent, caspase-3-dependent pathway. J Biol Chem 2001;276:49077-49082.
18. Canbay A, Friedman S, Gores GJ. Apoptosis: the nexus of liver injury and fibrosis. HEPATOLOGY 2004;39:273-278.
19. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: a systematic review. J Viral Hepat 2005;12:559-567.
20. Bodenheimer HC Jr, Lindsay KL, Davis GL, Lewis JH, Thung SN, Seeff LB. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. HEPATOLOGY 1997;26:473-477.