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The treatment of infectious disease with a medical device: results of a clinical trial of ultraviolet blood irradiation (UVBI) in patients with hepatitis C infection

J. Todd Kuenstner [a,b,*], Shanker Mukherjee [c], Stuart Weg [d], Trish Landry [e], Thomas Petrie [f]

[a] Clinical Laboratories, Charleston Area Medical Center, Charleston, Virginia, USA
[b] West Virginia School of Medicine, Charleston, West Virginia, USA
[c] Twin Rivers Gastroenterology Center, Easton, Pennsylvania, USA
[d] Franklin Lakes, New Jersey, USA
[e] M Squared Associates, Washington DC, USA
[f] AVIcure Bioscience LLC, Superior Quartz Products, Inc., Bethlehem, Pennsylvania, USA

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SUMMARY

Objectives: Prior to the advent of therapies with sustained virological response rates of 94%, this study was conducted for the US Food and Drug Administration (FDA) to assess the safety and efficacy of ultraviolet blood irradiation (UVBI) for the treatment of hepatitis C virus (HCV) infection.
Methods: Nine patients received 15 UVBI treatments over the course of 22 weeks with the AVIcure Hemo-modulator, which was modified from the original Knott Hemo-irradiator. The patients' viral loads and liver function tests were obtained periodically during the study and analyzed during the course of the trial.
Results: At the end of the study, the overall mean reduction in HCV viral load was 21.5% ($p = 0.023$); on day 140, direct bilirubin declined by 41.1% ($p = 0.0059$), aspartate aminotransferase declined by 15.2% ($p = 0.0069$), and alanine aminotransferase declined by 19.3% ($p = 0.0031$). The nadir of the mean and median viral load occurred on day 259, and it corresponded to a mean viral load reduction of 44.9% ($p = 0.0048$). During the course of the study, three patients had a greater than 0.5 log reduction in viral load (patient 1, 0.56 log reduction on day 259; patient 4, 0.69 log reduction at the end of the study; patient 11, 0.91 log reduction on day 259). Two patients showed marked improvement in their concurrent psoriasis at the conclusion of the trial.
Conclusions: In this study, UVBI was safe and had a beneficial effect in the treatment of HCV. This device should be studied for use in psoriasis and in infectious diseases that have few treatment options. This article describes a prospective, controlled, phase II clinical trial submitted to the FDA of this device used for the treatment of HCV infection (Investigational Device Exemption (IDE) #G030242).

1. Introduction

Before the advent of therapy for hepatitis C virus (HCV) infection with sustained virological response (SVR) rates of 94%,[1] ultraviolet blood irradiation (UVBI) was proposed as an adjunct to combination interferon and ribavirin in order to improve the SVR, which was 50%. This article describes the clinical trial of HCV patients that was submitted to the US Food and Drug Administration (FDA). After reviewing this clinical trial, the FDA allowed the sponsoring company to apply for a phase III pivotal trial. Although the phase III trial was never conducted, this trial is significant because of the potential efficacy of UVBI in the treatment of other infectious diseases with ineffective or nonexistent therapy.

UVBI was developed by Dr Emmet Knott in 1928,[2,3] after Finsen received the Nobel Prize in 1903 for his ultraviolet light therapy of the skin in patients with lupus vulgaris, i.e., tuberculosis of the skin.[4,5] Finsen described the treatment of 804 patients with tuberculosis of the skin and reported that 412 patients were cured (no recurrence during 2–6 years of observation in 124, or during an observation time of less than 2 years in 288), 192 patients were nearly cured, 117 were currently receiving treatment, and

* Corresponding author at: Clinical Laboratories, Charleston Area Medical Center, Charleston, 3200 MacCorkle Ave. SE, West Virginia, USA. Tel.: +1 304 388 4393.
E-mail address: jtodd.kuenstner@camc.org (J.T. Kuenstner).

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117 patients had interrupted their treatment (unsatisfactory result in 16, death in 44, and unaccounted for in 23 patients).[6]

Initially, the Knott device was used for the treatment of bacterial infections. Hancock described seven case histories of blood stream infection with positive blood cultures, one with colon bacillus (*Escherichia coli*), four with hemolytic streptococci, and two with staphylococci, who recovered following UVBI therapy alone.[7] Miley reported the case of a patient with *Staphylococcus aureus* septicemia who recovered following UVBI alone.[8] By 1944, Miley had described an additional 16 cases of staphylococcal septicemia treated with UVBI. He reported that seven consecutive patients who had *S. aureus* septicemia and failed sulfa drugs prior to UVBI died, but that nine consecutive patients with staphylococcal septicemia (*S. aureus* in six and *Staphylococcus albus* (*epidermidis*) in three) who had UVBI all recovered.[9] Wasson et al. subsequently conducted a 4-year study of UVBI used alone in rheumatic fever in 108 children, with 22 consecutive hospitalized cases of acute rheumatic fever and 86 cases of outpatient acute and subacute rheumatic fever.[10] They observed a rapid subsidence of the toxic symptoms in 20 of the 22 hospitalized patients, a more gradual recovery in one patient, and death in one patient. In all 107 surviving patients, they observed only two recurrences, a rate that compared favorably to sulfa compounds used prophylactically.

In a case series report of UVBI in eight patients with *E. coli* septicemia, six of the eight patients recovered and two patients died. Of the six who recovered, three had already failed sulfa drugs (cases 2, 7, and 8) and one surviving patient (case 1) had double septicemia with *E. coli* and hemolytic Streptococcus.[11]

Miley also described the use of UVBI in acute pyogenic infections.[12,13] He described 151 unselected, serial cases over the course of 3 years, with various acute pyogenic infections for which a majority received only UVBI and a minority were chemotherapeutic failures. He reported that 118 patients recovered and 33 patients died and that no patient with infection uncomplicated by septicemia progressed to a septicemia.[13] Miley and Rebbeck described the results of UVBI in a consecutive series of 72 patients critically ill with peritonitis. Forty-three of these patients received UVBI and 29 received UVBI after chemotherapeutic failure. Thirty-two of 40 patients with generalized peritonitis recovered, 17 of 20 cases of localized peritonitis recovered, and nine of 12 cases of peritonitis with multiple pelvic abscesses recovered. In the group of 29 that had already failed antibiotics, 20 subsequently recovered with UVBI.[14] Rebbeck and Lewis published a case series of six patients with typhoid fever who were treated with UVBI. The three patients who received sulfonamide and UVBI had an average recovery time of 51 days and the three patients who received UVBI alone had an average recovery time of 24 days. Of the three patients who received sulfonamide alone, two who survived had a recovery time of 78 days; the third patient in this group died.[15]

The Knott device was also used to treat viral infections. Miley and Christensen described the results of UVBI in 79 consecutive patients with acute viral infections including many cases of polio, a single case of herpes simplex, herpes zoster, and mumps. They reported rapid recovery following UVBI in the herpes and mumps cases as well as in the majority of polio cases.[16] In a case series report from 1955 that predated the identification of hepatitis A, B, and C, Olney described the results of UVBI in 43 patients with acute viral hepatitis. The patients were classified as either acute infectious hepatitis (31 patients) or acute serum hepatitis (12 patients), and following UVBI, a rapid subsidence of symptoms with decreasing liver function tests was noted.[17] By 1948, over 60 000 blood irradiations had been performed in the USA.[16]

In a controlled trial, Zhadnov et al. studied 222 patients with new onset destructive tuberculosis and found that of the 86 patients in the treatment group who received combination UVBI, electrophoresis, and antibiotics, bacterial discharge ceased in 100% and destruction in 89% within 3 months versus 59% and 38%, respectively, in the control group patients, who received antibiotics alone.[18] In the controlled trial reported by Shurygin comparing 25 patients on combination UVBI and antibiotics versus 37 patients on antibiotics alone, the patients receiving combination UVBI and antibiotics recovered more rapidly.[19]

Recently, Kuenstner et al. described several patients who were treated for infection by *Mycobacterium avium* subspecies *paratuberculosis* using combination UVBI and antibiotics, with resolution of Crohn's disease in one patient and complex regional pain syndrome in another patient.[20]

Prior to the development of the treatment protocol used in this study, a preliminary study of two patients with HCV infection treated with a predecessor UVBI device showed substantial reductions in viral load and liver function tests accompanied by symptomatic improvement. The results are shown in Table 1. For patient A, the viral load tests were done at Specialty Laboratories Inc. (Santa Monica, CA, USA) with the PCR RNA Ultraquant method and the reference range was <200 copies/ml. For patient B, the viral load tests were done at Medical Diagnostic Laboratories LLC (Mount Laurel, NJ, USA) by PCR and the reference range was <100 HCV copies/ml serum. Based on these observations and on the previously cited literature, a phase II study for the FDA was designed and conducted as described below.

Table 1
Preliminary observations for two cases treated with UVBI

Patient	Baseline viral load (copies/ml)	Final viral load (copies/ml)	Method reference range (copies/ml)	Treatment period
A	2464	<200	<200	8 days
B	652 800	Not detectable	<100	109 days

UVBI, ultraviolet blood irradiation.

2. Methods

Pilot Study #2 for the Hemo-Modulator for the Reduction of Viral Load in Patients with Chronic Hepatitis C (CHC) began in March 2006 under the IDE protocol approved by the FDA in Supplement 8 on February 21, 2006, and was approved by the Warren Hospital Institutional Review Board (IRB). The single investigational site was Warren Hospital, Phillipsburg, NJ, USA.

The inclusion criteria for the trial included the following: (1) a diagnosis of CHC confirmed by the presence of the antibody to HCV virus (anti-HCV) by enzyme immunoassay (EIA), and by a positive anti-HCV by recombinant immunoblot assay (RIBA); (2) a positive HCV-RNA by reverse transcriptase PCR (RT-PCR) for at least 6 months; (3) subject classified as a non-responder. A non-responder was defined as a patient who had detectable HCV-RNA upon completion of a course of standard pharmacological treatment (interferon plus ribavirin) or who had failed to maintain undetectable HCV-RNA for 6 months following the end of treatment for a standard course of pharmacological treatment.

The exclusion criteria for the trial included the following: (1) the subject had cirrhosis, hepatocellular carcinoma, or another liver disease; (2) the subject habitually used excessive alcohol or illicit drugs; (3) the subject had had a positive test for HIV confirmed by Western blot obtained within the past 12 months.

Eleven subjects were enrolled in the study and nine completed the treatment regimen. The patients served as their own controls. Subjects underwent three sessions of five ultraviolet blood irradiation treatments over a 22-week period, with a 6-month

Table 2
Treatment schedule

Week	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1, 10, 20				Treatment 1		Treatment 2	
2, 11, 21		Treatment 3				Treatment 4	
3, 12, 22				Treatment 5			

post-treatment follow-up period. The treatment schedule followed the original Knott protocol and is shown in Table 2.

The primary effectiveness measurement of the study was complete clearance of the virus by the end of the treatment period. The secondary effectiveness measurements included a reduction in viral load and a decrease in tests of inflammation of the liver (direct bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)). Both the viral load and the liver function tests were assessed in two ways: (1) individual improvement, and (2) overall group improvement.

The primary effectiveness measurements of UVBI treatment with the Hemo-modulator included a comparison of the baseline viral load to the viral load at 6 months following the last treatment for each subject, measured by RT-PCR. Clinical success was defined as at least 10% of the patients treated (on an intent-to-treat basis) achieving an undetectable HCV-RNA level (<40 IU/ml serum) at the end of treatment (week 22) and maintaining that undetectable level for 6 months after the last treatment.

A secondary assessment of effectiveness was performed at the end of the study. The following endpoints were assessed: (1) percentage of patients achieving a negative HCV-RNA level at each follow-up point, (2) percentage of patients achieving negative HCV-RNA at week 22, who maintained undetectable levels through week 46, and (3) percentage of patients achieving normal liver function tests at each follow-up point.

The direct bilirubin, AST, and ALT tests were done at the Warren Hospital laboratory on a Dimension RxL Analyser (Dade Behring Corp., later acquired by Siemens Healthcare Diagnostics, Inc., Newark, DE, USA). The reference ranges were 14–38 IU/l for AST, 24–50 IU/l for ALT, and 0–0.3 mg/dl for direct bilirubin. HCV viral load testing was done at the Laboratory Corporation of America (Raritan, NJ, USA). The method used was RT-PCR and the detection limit was 40 IU/ml serum.

2.1. The AVIcure Hemo-irradiator

The original Knott Hemo-irradiator was redesigned to meet contemporary safety standards. The lamp was designed to generate wavelengths between 200 nm and 400 nm, which encompass the germicidal bands of UVB (280–315 nm) and UVC (200–280 nm). In addition to the lamp, a light chamber in the device was engineered to provide consistent exposure among treatments.

A peristaltic pump that does not come into contact with the patient's blood creates a regulated blood flow and reinfusion. Blood contact only occurs within the enclosed disposable kit. The disposable kit consists of a reservoir bag and tubing connected to a blood exposure chamber. The reservoir bag allows for rapid blood drawing and paced reinfusion, and the blood exposure chamber provides maximum lamp exposure to the passing blood surface. The blood passes through the exposure chamber, a continuous spiral labyrinth that exposes the blood to the UV light. This efficient design provides maximum exposure to the treated blood surface. The kit was designed to produce less than 0.07% hemolysis during the treatment. The volume of treated blood is based on patient weight, i.e., 1.5 cc/lb (3.3 ml/kg).

Blood is collected into a vacuum sterile container prepared with 3000 to 5000 units of heparin sodium. The container is carefully inverted to mix the blood with the heparin and then hung from an intravenous (IV) pole attached to the UVBI system. The blood is then circulated through the exposure chamber, thereby exposing the blood to UV irradiation at a rate of approximately 30 ml/min. The irradiated blood is then returned to the patient at the fastest infusion rate allowed (per a standard administration set). The duration of the procedure is approximately 20 min.

3. Results

Nine patients completed the treatment regimen and each received 15 Hemo-modulator treatments. The data from these patients are presented as the primary data set. Since patient 2 completed 12 of the planned 15 treatments, the data obtained for this patient are included in several of the analyses as well. Each of the pre-established success criteria and an analysis of the study results against these criteria are presented next. With respect to the primary effectiveness criteria stated above, no patient achieved an undetectable HCV-RNA level at the end of treatment (week 22) or at any time recorded throughout the study. With respect to the secondary effectiveness criteria stated above, the following results were observed. A one-tailed *t*-test for paired samples ($\alpha = 0.05$) was used for the statistical analyses in Tables 3–6.

3.1. Individual improvement in viral load

Three patients had a greater than 0.5 log reduction in viral load. Patient 4 exhibited a 0.69 log reduction at the end of the study (Table 3). On day 259, patient 1 exhibited a 0.56 log reduction and patient 11 exhibited a 0.91 log reduction (Table 4).

3.2. Overall improvement in viral load

Table 3 shows that there was a mean reduction of 21.5% in the viral load ($p = 0.023$) at the end of the study. Note that a tenth patient (patient 2, who completed 12 of the 15 treatments) is included in this analysis. Figure 1 shows the variation in mean and median viral load during the study. From day 0 through 150, the mean and median viral load increased and then after day 150, it steadily declined. The nadir of the mean and median viral load occurred on day 259, and it corresponded to a mean viral load reduction of 44.9% ($p = 0.0048$). Note that a tenth patient (patient 2, who completed 12 of the 15 treatments) is included in this analysis.

3.3. Individual improvement in liver function tests

Individual liver function results did not meet the secondary assessment of effectiveness criterion, i.e., normalization of liver function tests. All patients with the exception of patients 3, 6, 7, and 13 began the study with elevated AST and ALT and did not experience a normalization of AST or ALT at any study time point. The only normalization of a liver function test occurred in patient 4 for direct bilirubin. Note that only one patient began the study

Table 3
Percentage change and log change in viral load, comparing the baseline to the end of study viral load. The baseline viral load was the average of the viral loads on days −14 and 0, while the end of study viral load was the average of the viral loads on days 323 and 327[a]

Patient	Baseline viral load (IU/ml)	Final viral load (IU/ml)	% Change in viral load	Baseline log viral load	Final log viral load	Change in log viral load
1	1 560 000	535 000	−65.71%	6.193	5.728	−0.46
2	5 665 000	5 630 000	−0.62%	6.753	6.751	−0.0027
3	1 028 500	1 107 500	+7.68%	6.012	6.044	+0.032
4	2 530 000	518 000	−79.53%	6.403	5.714	−0.69
6	739 500	1 050 500	+42.06%	5.869	6.021	+0.15
7	3 010 000	2 925 000	−2.82%	6.479	6.466	−0.012
9	3 140 000	2 730 000	−13.06%	6.497	6.436	−0.061
11	657 500	313 500	−52.32%	5.818	5.496	−0.32
12	3 095 000	2 685 000	−13.25%	6.491	6.429	−0.062
13	4 040 000	2 525 000	−37.50%	6.606	6.402	−0.20
Mean	2 546 550	2 001 950	−21.51%	6.312	6.145	−0.163

[a] Change in viral load: $p = 0.023$, t-statistic = −2.31. Change in log viral load: $p = 0.038$, t-statistic = −1.99.

Table 4
Percentage change and log change in viral load, comparing the baseline to the nadir of the viral load. The baseline viral load was the average of the viral loads on days −14 and 0, while the nadir of the viral load occurred on day 259 of the study. Patients 2, 6, and 13 were omitted because they did not have any viral load data for this date[a]

Patient	Baseline viral load (IU/ml)	Nadir viral load (IU/ml)	% Change in viral load	Baseline log viral load	Nadir log viral load	Change in log viral load
1	1 560 000	429 000	−72.5	6.19	5.63	−0.56
3	1 028 500	1 260 000	+22.5	6.01	6.10	+0.09
4	2 530 000	937 000	−63.0	6.40	5.97	−0.43
7	3 010 000	2 010 000	−33.2	6.47	6.30	−0.18
9	3 140 000	2 380 000	−24.2	6.49	6.37	−0.12
11	657 500	81 800	−87.6	5.81	4.91	−0.91
12	3 095 000	1 350 000	−56.4	6.49	6.13	−0.36
Mean	2 145 857	1 206 829	−44.9	6.26	5.92	−0.35

[a] Change in viral load: $p = 0.0048$, t-statistic = −3.73. Change in log viral load: $p = 0.015$, t-statistic = −2.85.

with elevated direct bilirubin, so the normalization of direct bilirubin was not possible for the other patients.

Although the normalization of AST and ALT did not occur for any patient, consistent and modest declines were observed for some patients. As shown in Table 5, five patients showed declines in all three liver function tests at the end of the study (patients 1, 3, 4, 9, and 13). On day 140, the nadir of the liver function tests, six patients had declines in all three liver function tests (patients 1, 3, 4, 7, 9, and 13) (Table 6).

3.4. Overall improvement in liver function tests

Figure 2 shows that the nadir of the decline in liver function occurred on day 140 rather than at the end of the trial. Table 6 shows that for the group as a whole on day 140, direct bilirubin declined by 41.1% ($p = 0.0059$), AST declined by 15.2% ($p = 0.0069$), and ALT declined by 19.3% ($p = 0.0031$). Modest declines in liver function tests were observed at the end of the study as well. Direct bilirubin declined by 31.4% ($p = 0.0016$), AST declined by 24.9% ($p = 0.066$), and ALT declined by 17.9% ($p = 0.105$).

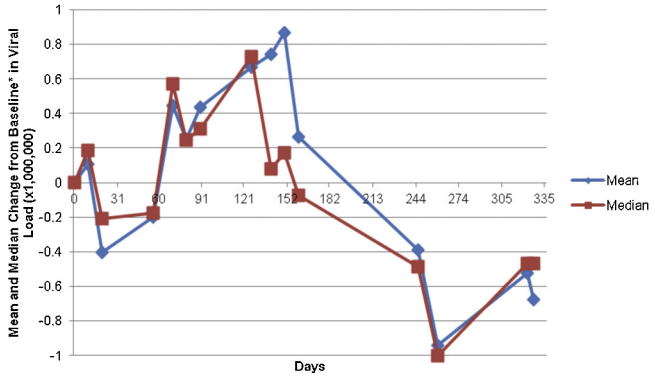

Figure 1. Variation in the mean and median viral load over time.

3.5. Serious adverse events (AEs)/unanticipated adverse device effects (UADEs)

Side effects were generally mild and resolved on their own or with minimal medical attention. The compliance of the patients in this trial, who all completed all 15 treatment visits on schedule, even though some had to travel long distances, further demonstrates that Hemo-modulator treatments are very well tolerated by patients. A summary of the side effects appears in Table 7.

3.6. Additional findings

Two patients experienced unanticipated health improvements. They had mild to severe psoriasis that was unresponsive to other therapies. Both subjects were noted to have a dramatic improvement in their psoriasis with the UVBI treatments and both were clear for several months after completion of the full course of UVBI. One of the two patients (patient 1) had complete remission of their psoriasis, which had been present for several years. The symptoms resolved during treatment, reappeared briefly after treatment cessation, and then resolved completely for the duration of the follow-up period. The patient was still free of psoriasis as of June 2007, which was more than 9 months from his last UVBI treatment.

4. Discussion

This prospective controlled study of nine patients with HCV infection demonstrates that UVBI used without other therapy was

Table 5
Percentage change in liver function tests, comparing the baseline to the end of study liver function markers. For each respective liver function test, the baseline was the average of days −14 and 0, while the end of study was the value of the liver function tests on day 327[a]

Patient	Baseline direct bilirubin (mg/dl)	Final direct bilirubin (mg/dl)	% Change direct bilirubin	Baseline AST (U/l)	Final AST (U/l)	% Change AST	Baseline ALT (U/l)	Final ALT (U/l)	% Change ALT
1	0.15	0.1	−33.3	85	53	−37.6	156	104	−33.3
2	0.1	0.1	0	63	45	−28.6	125	77	−38.4
3	0.2	0.1	−50.0	33	31	−6.1	79	62	−21.5
4	0.35	0.3	−14.3	50	30	−40.0	81	65	−19.8
6	0.1	0.1	0	46	40	−13.0	74	68	−8.1
7	0.1	0.1	0	28	11	−60.7	49	38	−22.4
9	0.2	0.1	−50.0	118	64	−45.8	282	159	−43.6
11	0.15	0.1	−33.3	126	159	26.2	204	233	14.2
12	0.3	0.2	−33.3	128	136	6.3	221	279	26.2
13	0.1	0	−100.0	28	14	−50.0	66	45	−31.8
Mean	0.175	0.12	−31.4	70.5	58.3	−24.9	133.7	113	−17.9

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a] Liver function tests: direct bilirubin $p = 0.0016$, t-statistic = −3.97; AST $p = 0.066$, t-statistic = −1.66; ALT $p = 0.105$, t-statistic = −1.35.

Table 6
Percentage change in liver function tests, comparing the baseline to the nadir of the liver function tests. For each respective liver function test, the baseline was the average of days −14 and 0, while the nadir of the liver function tests occurred on day 140[a]

Patient	Baseline direct bilirubin (mg/dl)	Nadir direct bilirubin (mg/dl)	% Change direct bilirubin	Baseline AST (U/l)	Nadir AST (U/l)	% Change AST	Baseline ALT (U/l)	Nadir ALT (U/l)	% Change ALT
1	0.15	0.1	−33.3	85	55	−35.3	156	95	−39.2
2	0.1	0.1	0	63	40	−36.6	125	87	−30.4
3	0.2	0.1	−50.0	33	29	−12.2	79	68	−14.0
4	0.35	0.2	−42.9	50	48	−4.0	81	70	−13.6
6	0.1	0.1	0	46	31	−32.7	74	59	−20.3
7	0.1	0	−100.0	28	27	−4.0	49	42	−14.3
9	0.2	0.1	−50.0	118	93	−21.2	282	224	−21.6
11	0.15	0.2	+33.3	126	125	−1.0	204	169	−17.2
12	0.3	0.1	−67.7	128	126	−2.0	221	225	+2.0
13	0.1	0	−100.0	28	22	−2.5	66	50	−24.3
Mean	0.175	0.1	−41.1	70.5	59.6	−15.2	133.7	108.9	−19.3

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a] Liver function tests: direct bilirubin $p = 0.0059$, t-statistic = −3.14; AST $p = 0.0069$, t-statistic = −3.05; ALT $p = 0.0031$, t-statistic = −3.55.

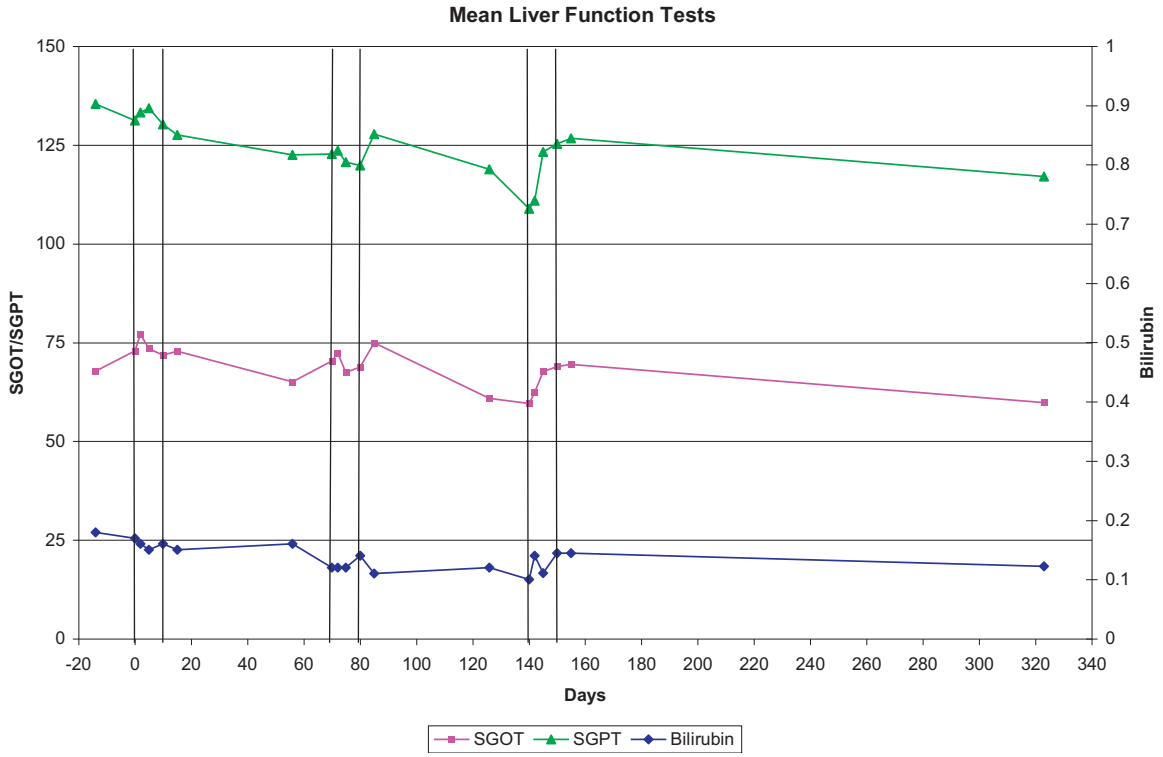

Figure 2. Variation in the mean liver function tests over time.

Table 7
Summary of anticipated and unanticipated adverse effects

Anticipated and unanticipated adverse effects	Frequency
Serious and/or unanticipated adverse events	
Vasovagal episode	1
Porphyria cutanea tarda (determined not due to UVBI)	1
Adverse events	
Headache	1
Hot flashes	3[a]
Body rash	1
Urinary tract infection	1
Hematoma at post treatment lab access site	1

UVBI, ultraviolet blood irradiation.
[a] All three for the same patient (patient 7).

safe. In addition, it was effective and caused a significant reduction in HCV viral load and a reduction in inflammatory markers. During the course of the study, three patients had a greater than 0.5 log reduction in viral load (patient 1, 0.56 log reduction on day 259; patient 4, 0.69 log reduction at the end of the study; patient 11, 0.91 log reduction on day 259). These results are unlikely due to expected random fluctuation in viral load. HCV-RNA rarely varies by more than 1 log and in most cases the variation is less than 0.5 log.[21] For the entire group, by the end of the study, there was a reduction in HCV viral load of 21.5% ($p = 0.023$); on day 140, direct bilirubin declined by 41.1% ($p = 0.0059$), AST declined by 15.2% ($p = 0.0069$), and ALT declined by 19.3% ($p = 0.0031$). For many of the patients (patients 1, 3, 4, 9, and 13), declines in the viral load occurred with declines in all three liver function tests.

A proper analysis of these results would compare UVBI to monotherapy such as sofosbuvir or lepidasvir used alone. In this scenario, although treatment with sofosbuvir results in HCV viral load declines of 5 to 6 log, this therapy is also subject to treatment failure when used alone due to the development of viral resistance.

The mechanism of action of UVBI is incompletely understood. Ultraviolet light in the C region (UVC) inactivates bacterial and viral pathogens present in the blood that is irradiated. In the case of bacteria and DNA viruses, UVC induces the formation of thymine–thymine dimers that prevent replication.[22] In the case of RNA viruses, UVC induces the formation of uracil–uracil dimers that also prevent replication.[23] Bacteria can repair ultraviolet light-induced damage and normal lymphocytes also have repair mechanisms.[24,25]

Because only 200 ml of blood in an average adult (or 4% of the total 5.0-l blood volume) is treated during a session of UVBI, factors other than pathogen inactivation, such as enhancing innate immunity, are likely responsible for the benefit. A detailed discussion of potential mechanisms of action is found in an article by Kuenstner et al.[20]

Two of the patients in this trial had concurrent psoriasis and showed marked improvement in this condition by the end of the trial. A clinical trial of UVBI is planned for patients with psoriasis.

Based on this prospective clinical trial in hepatitis C infection and the numerous case series reports in other infectious diseases, this device should be studied as a standalone or adjunctive therapy for infectious diseases that emerge and for others without effective therapy. Such diseases include multidrug-resistant *Mycobacterium tuberculosis*, multidrug-resistant *Salmonella typhi*, *Mycobacterium avium* complex including subspecies *paratuberculosis*, and dengue, chikungunya, Ebola, Marburg, West Nile, and influenza viruses. A study of the efficacy of UVBI in monkeys infected with simian immunodeficiency virus has been performed and showed positive results; this will be submitted for publication. Finally, further studies using UVBI adjunctively to treat human infection with *Mycobacterium avium* complex including subspecies *paratuberculosis* will be conducted in the near future.

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Compliance with ethics guidelines: The animal and human studies that are described in this article were conducted in compliance with guidelines from the appropriate regulatory agencies. This study was approved by the Warren Hospital Institutional Review Board.

Conflict of interest: Kuenstner and Petrie are shareholders in AVIcure Bioscience, LLC, which has a proprietary interest in the UVBI device and disposables used in this study.

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