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INFECTIOUS DISEASES | RESEARCH ARTICLE

A controlled clinical trial of ultraviolet blood irradiation (UVBI) for hepatitis C infection

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Abstract: The FDA Phase I controlled clinical trial results of ultraviolet blood irradiation (UVBI) to treat patients with hepatitis C Virus (HCV) infection are described in this report. This study was conducted prior to the availability of other highly effective therapies, e.g., the combination of ledipasvir and sofosbuvir (Gilead Sciences, Inc.). Five UVBI treatments were administered to 10 patients in 3 weeks. Viral loads and markers of hepatic inflammation were assessed before and after treatment. The patients were treated with a modified Knott Hemo-Irradiator (AVIcure Bioscience, LLC). After five treatments in nine of the patients, the mean percentage change in viral load was -56.0% and the mean change in log viral load was -0.60 ($p = 0.017$). During the study, seven of 10 patients demonstrated a > 0.49 log reduction in viral load. There were no significant adverse events. UVBI was safe in all patients and effective for the treatment of HCV infection in a majority of patients (IDE #G030242). This device should be studied for the treatment of other infectious diseases for which there are few treatment options.

Subjects: Biomedical Engineering; Health Conditions; Medicine

Keywords: Ultraviolet blood irradiation; Crohn's disease; tuberculosis; hepatitis C virus

ABOUT THE AUTHOR

J. Todd Kuenstner's research is focused on determining the scope of autoimmune diseases caused by *Mycobacterium avium* ssp. *paratuberculosis* (MAP). In addition, Kuenstner is studying chronic inflammatory diseases for causation by pathogens other than MAP. He is especially interested in non-pharmacologic therapies for infectious disease, e.g., Ultraviolet Blood Irradiation (UVBI). The research in this article will be used to support the application of UVBI for MAP infection and other infectious diseases that lack effective curative therapies.

PUBLIC INTEREST STATEMENT

In recent years, the resistance of bacteria and viruses to antibiotics and anti-viral drugs has become a major threat to effective disease treatment. Simultaneously, few new antibiotics are under development in comparison to the number of new candidates having chronic immune suppressive therapies. Finally, newly recognized pathogens continue to emerge. Emergence of new pathogens and resistance to existing therapies will continue indefinitely. UVBI is an important way to address this ongoing public health threat.

UVBI is used widely in complementary medicine clinics in the United States, but there are no FDA (or ex-United States equivalent agency) approved UVBI devices in use. These devices vary greatly in design and performance characteristics and there are no protocols for the treatment of specific infection supported by controlled clinical trial data. The goal of this research is to establish treatment protocols supported by controlled clinical trials.

1. Introduction

Prior to the development of therapy with sustained virological response (SVR) rates of 94% (Kv et al., 2014), combination ribavirin and interferon for the treatment of hepatitis C virus (HCV) infection had a SVR of 50%. To improve the unsatisfactory SVR, ultraviolet blood irradiation (UVBI) was considered a promising therapy and a potential adjunct to combination interferon and ribavirin. The results of the US Food and Drug Administration (FDA) Phase I controlled clinical trial for the treatment of HCV infection with UVBI are presented in this article. Previously, the FDA Phase II controlled clinical trial for UVBI showed therapeutic benefit in patients infected with HCV (Kuenstner, Mukherjee, Weg, Landry, & Petrie, 2015). However, the phase II trial used a different treatment protocol than described in this trial, and these differences have important implications for the design of future clinical trials. After reviewing the results of the phase I and phase II trials, the sponsor was permitted by the FDA to make an application for a pivotal trial. The pivotal trial did not occur, but the trial in this report has implications for the treatment of infectious diseases other than HCV, for which there are no effective treatments.

Emmett Knott invented UVBI in 1928 (Hancock & Knott, 1934; Knott, 1948), but the use of ultraviolet light for the treatment of infectious disease was originally proposed by Niels Finsen at the turn of the century. Finsen won the Nobel Prize in 1903 for treating lupus vulgaris—i.e. tuberculosis of the skin—with ultraviolet light therapy of the skin (Finsen, 1902; Niels Ryberg Finsen_bio, 2014). Half of Finsen's patients (412 of 804) were cured, which was defined as no recurrence during 2–6 years observation in 124 patients, and for the other 288 patients, no recurrence in less than 2 years. Additionally, 192 patients were almost cured, 117 patients were undergoing treatment, and 117 patients had interrupted treatment (44 patients died, 16 patients had unsatisfactory results, and 23 patients were not accounted for) (Gotzsche, 2011).

Knott's device was originally used to treat bacterial infections. In a case series of seven patients with bloodstream infections and accompanying positive blood cultures (one with colon bacillus (*Escherichia coli*); two with staphylococci; and four with hemolytic streptococci), Hancock reported recovery after UVBI monotherapy (Hancock, 1942). In another case report, Miley described a patient with *Staphylococcus aureus* septicemia who recovered after UVBI monotherapy (Miley, 1943). Miley later reported another 16 cases of *staphylococcus* septicemia successfully treated with UVBI. Nine consecutive patients (three with *Staphylococcus albus* (*epidermidis*) and six with *S. aureus*) were treated with UVBI and all recovered, while the remaining seven consecutive patients, who had failed sulfa drugs before UVBI treatment, died (Miley, 1944). In a subsequent report, Wasson et al. used UVBI in a 4-year study to treat 108 children with rheumatic fever (86 cases of outpatient acute and subacute rheumatic fever, and 22 consecutive hospitalized cases of acute rheumatic fever) (Wasson, Miley, & Dunning, 1950). Of the latter group, 20 patients experienced a swift decline in toxic symptoms, while one patient gradually recovered and another died. Only two recurrences occurred in the 107 surviving patients, which was a rate comparable to that of prophylactically administered sulfa drugs.

A case series of eight patients with *E. coli* septicemia reported that, following UVBI treatment, six patients recovered and two patients died. Notably, of the six recovered patients, three had previously failed sulfa drugs and one had double septicemia with hemolytic *Streptococcus* and *E. coli* (Rebeck, 1942).

UVBI was also used by Miley to treat acute pyogenic infections (Miley, 1942a). In a 3-year period, Miley described 151 random, serial cases with varying acute pyogenic infections, the majority of which were treated with UVBI monotherapy successfully (a minority were chemotherapeutic failures). Miley reported recovery in 118 patients, death in 33, as well as that no patient with an infection uncomplicated by septicemia developed a septicemia (Miley, 1942b). In 72 consecutive patients, Miley and Rebeck reported treating peritonitis with UVBI, and in 29 cases, they had failed antibiotics. In this group of 29 chemotherapeutic failures, 20 recovered following UVBI treatment (Miley & Rebeck, 1943). Furthermore, they observed recovery in 17 of 20 cases of

localized peritonitis, 32 of 40 cases of generalized peritonitis, and nine of 12 cases of peritonitis featuring multiple pelvic abscesses. In another case series, Rebbeck and Lewis described six cases of typhoid fever treated with UVBI. The recovery time was expedited in the three patients who received UVBI monotherapy versus the three patients who received combination sulfonamide and UVBI (24 days and 51 days, respectively). Three patients also received sulfonamide alone, two of whom had a recovery time of 78 days; the last patient died (Rebbeck & Lewis, 1949).

Though the Knott device was initially used to treat bacterial infections, it was also used to treat viral infections. Miley and Christensen treated 79 consecutive patients with acute viral infections, including mumps, herpes zoster, herpes simplex, and numerous cases of polio. Following UVBI treatment, they observed rapid recovery in most polio cases as well as in the mumps and herpes cases (Miley & Christensen, 1948). In a 1955 case series report by Olney, which predated hepatitis subtype classification, 43 cases of acute viral hepatitis were treated with UVBI. Thirty-one patients were classified as acute infectious hepatitis and 12 patients were classified as acute serum hepatitis. Olney observed a swift subsidence of symptoms and decreasing liver inflammatory markers following UVBI treatment (Olney, 1955). By the late 1940s, in excess of 60,000 UVBI treatments had been administered in the United States, but the treatment fell into obscurity with the advent of the antibiotic age (Miley & Christensen, 1948).

More recently, in a controlled trial consisting of 222 patients with new onset destructive tuberculosis, Zhadnov et al. treated patients with combination antibiotics, electrophoresis, and UVBI or antibiotics alone. In the former group, within 3 months, bacterial discharge ceased in 100% of patients and destruction in 89% versus 59% and 38%, respectively, in the latter group (Zhadnov, Mishanov, Kuznetsov, Shprykov, & Ryzhakova, 1995). In another controlled trial for pulmonary tuberculosis, Shurygin treated 25 patients with combination antibiotics and UVBI and 37 patients with antibiotics alone. Shurygin reported a more rapid recovery for patients who received combination antibiotics and UVBI (Shurygin, 2009).

Most recently, Kuenstner et al. treated two patients for infection by *Mycobacterium avium* ssp. *paratuberculosis* (MAP) with combination antibiotics and UVBI, and observed resolution of Crohn's disease in one patient and complex regional pain syndrome in the other patient (Kuenstner et al., 2015; Kuenstner, Naser, & Chamberlin et al., 2017)

Kuenstner et al. also reported significant reductions in viral load and liver inflammatory markers in the phase II trial of UVBI for HCV infection (Kuenstner et al., 2015). Notably, the phase II trial, while encouraging, brought to light important methodological considerations for future clinical trials. This report describes the FDA phase I clinical trial and the UVBI methodology.

2. Methods

The investigational site for the study was Warren Hospital, Phillipsburg, NJ, USA. The protocol was approved by the Warren Hospital Institutional Review Board (IRB) following approval by the FDA on 21 February 2006 in Supplement 8. All subjects gave informed consent and the trial was conducted in accordance with the Declaration of Helsinki.

This trial was not registered in a public clinical trial registry for the following reason. Although ClinicalTrials.gov was established in 2000, it was initially used to inform the public about drug trials for serious or life-threatening conditions. There was no provision for medical device trials to be included and the database almost exclusively included NIH sponsored trials. In 2005, the International Committee of Medical Journal Editors (ICMJE) began requiring trial registration as a condition of publication, but trial registration was not required by the FDA at that time.

The following criteria had to be met for a subject's inclusion in the study: a chronic hepatitis C (CHC) diagnosis confirmed by a positive anti-HCV antibody test via the enzyme immunoassay (EIA) method and by the recombinant immunoblot assay (RIBA) method; the presence of HCV-RNA

for 6 months or more, confirmed by reverse transcriptase PCR (RT-PCR); subjects were non-responders. To be considered a non-responder, a subject either had detectable levels of HCV-RNA following standard pharmacologic treatment (combination interferon and ribavirin) or did not maintain undetectable levels of HCV-RNA in the 6-month period after the standard pharmacologic treatment.

Subjects with a positive HIV test from the past 12 months (confirmed by Western blot), hepatocellular carcinoma, cirrhosis, or other liver disease were excluded from the study. Subjects who habitually ingested excessive alcohol or used illicit drugs were also excluded from the study.

The primary effectiveness measurement of UVBI was a 25% decrease in viral load. The baseline viral load was the mean of three separate tests from blood drawn on days 1, 3, and 7. The final viral load was the mean of three separate tests obtained at week 8, week 9 and week 10. A viral load measurement was also obtained 3 days after treatment 5 for nine of the patients. The secondary effectiveness measurement was an improvement in AST and ALT in the post-treatment versus baseline tests. The AST and ALT were obtained at the 8-week follow-up for patients 1 through 8 and at 3 days after treatment 5 for patients 9 through 12.

While there were numerous similarities between the phase II trial previously reported and the phase I trial described here, there were important methodological differences between both trials (Figure 1). The phase I trial consisted of five treatments in 3 weeks, with a post-treatment viral load test obtained 3 days after treatment 5 for nine of the patients. In contrast, the phase II trial consisted of three 3-week treatment periods of five treatments, separated by two 7-week periods with no treatment. The final viral load was obtained 6 months following the last treatment. Consequently, the phase II trial had lengthy periods of time without treatment prior to measurement of the final viral load.

A brief description of the modified Knott Hemo-Irradiator (AVIcure Bioscience, LLC.) follows. The treatment procedure is performed in approximately 20 min. The blood volume and time needed for the treatment is determined by the protocol formula, 1.5 cc per pound of patient weight, and the time needed to collect the blood. The device processes the patient’s blood at a fixed flow rate of 30 mL/min, and the total time is dependent on the volume of blood collected (approximately 200 cc). The blood exposure time is controlled by the fixed 30 mL/minute flow rate and a 72 rpm chopper window, which exposes the blood to 8-s intervals of 4 mw/cm² of ultraviolet light energy.

Twelve patients enrolled in the study, and 10 patients received all treatments according to the Knott protocol in Table 1. Each patient served as their own control. Using SAS software (Statistical Analysis System software program, SAS, Cary, North Carolina), a Wilcoxon signed ranks test for paired samples was used to compare viral load and hepatic inflammation markers at baseline to later time points of interest. All tests were conducted at the 0.05 level of significance. The markers of hepatic inflammation (AST and ALT) and the HCV viral load testing, along with reference ranges, are described in the prior report (Kuenstner et al., 2015).

Figure 1. Study timeline highlighting the methodological differences between (a) the previously published FDA Phase II clinical trial and (b) the FDA Phase I clinical trial described here.

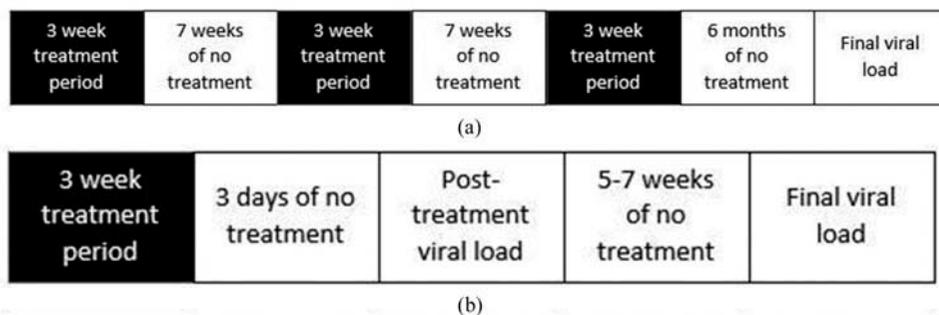


Table 1. FDA phase I clinical trial treatment schedule of UVBI in patients with HCV infection

Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1				Tx		Tx	
2	Tx					Tx	
3				Tx			

*Tx denotes a UVBI treatment session.

3. Results

Table 2 shows that after five treatments, there was a mean viral load percentage change of -56.0% and a mean viral load log change of -0.60 ($p = 0.017$) and six of 10 patients exhibited more than a 0.49 log decrease in viral load. Table 3 shows that an additional patient had a further reduction in log viral load from 0.36 after five treatments to 0.53 by the end of the study. Additionally, Table 3 demonstrates a decrease of 0.34 in the log viral load ($p = 0.093$) at the study's conclusion and that five of the patients had declines in AST and ALT, but the mean declines of 3.7% in AST ($p = 0.374$) and 4.3% in ALT ($p = 0.284$) did not reach the level of significance.

Although the number of patients enrolled in the trial was small, there were no significant adverse events. However, patient 1 experienced two episodes of headache (after treatments 1 and 4); patient 2 experienced mild dizziness upon standing (after treatment 2) and headache (after treatment 3); patient 7 experienced two episodes of headache (after treatments 1 and 2). All headaches resolved within 24 h.

4. Conclusion

This FDA Phase I controlled clinical trial of 10 patients demonstrates that UVBI used without other therapy significantly reduced the hepatitis C viral load. It is not likely that this viral load reduction resulted from random fluctuation, because in most patients, the variation of HCV RNA is less than 0.5 logs (Nguyen et al., 1996). Six of 9 patients after five treatments (seven of 10 by the study's conclusion) showed more than a 0.49 log decrease in viral load during the study.

This phase I trial met the primary effectiveness criterion of a reduction of greater than 25% in viral load. The reduction in viral load was greater after five treatments than at the end of the study, and this

Table 2. FDA Phase I Clinical Trial results of UVBI in HCV infected patients after five treatments

Patient	Viral load baseline (IU/ml)	Viral load post Tx5 (IU/ml)	Percentage change in viral load	Baseline log viral load	Post 5Tx log viral load	Log change in viral load
1	3,402,333	1,490,000	-56.2	6.53	6.17	-0.36
2	142,333	207,000	+45.4	5.15	5.32	+0.16
3	21,703,333	1,810,000	-91.7	7.34	6.26	-1.08
4	1,916,667	169,000	-91.2	6.28	5.23	-1.05
7	15,133,333	4,380,000	-71.1	7.18	6.64	-0.54
8	1,245,667	1,250,000	+0.34	6.10	6.10	0
10	13,666,667	4,410,000	-67.8	7.14	6.64	-0.49
11	1,607,000	382,000	-76.2	6.21	5.58	-0.62
12	51,100,000	2,140,000	-95.8	7.71	6.33	-1.38
Mean	12,213,037	1,804,222	-56.0	6.63	6.03	-0.60
p-value		0.021				0.017
z-statistic		-2.310				-2.380

*Note that patients 5 and 6 dropped out of the study and that there is no data at post 5 treatments for patient 9.

Table 3. FDA phase I clinical trial results of UVBI in HCV infected patients, comparison of viral load at the beginning and end of the trial and comparison of AST and ALT during the trial

Patient	Baseline viral load (IU/ml)	Final viral load (IU/ml)	Log change in viral load	Pre AST	Post AST	% change AST	PreALT	Post ALT	% change ALT
1	3,402,333	1,007,000	-0.53	42	32	-23.8	66	60	-9.1
2	142,333	90,400	-0.20	189	142	-24.9	440	319	-27.5
3	21,703,333	7,536,667	-0.46	37	27	-27.0	75	61	-18.7
4	1,916,667	97,433	-1.29	45	41	-8.9	139	109	-21.6
7	15,133,333	2,169,000	-0.84	25	26	+4.0	64	65	+2.0
8	1,245,667	2,996,667	+0.38	56	68	+21.4	98	90	-8.2
9	711,333	2,357,333	+0.52	37	34	-8.1	56	72	+28.6
10	13,666,667	13,710,000	0	71	106	+49.3	94	125	+33.0
11	1,607,000	726,000	-0.35	18	18	0	30	26	-13.3
12	51,100,000	11,000,000	-0.67	75	61	-18.7	101	93	-7.9
Mean	11,062,867	4,169,050	-0.34	60	56	-3.7	116	102	-4.3
p-value		0.074	0.093		0.374			0.284	
z-stat.		-1.784	-1.682		-0.89			-1.07	

difference is probably due to the absence of therapy during the period when weeks 8, 9 and 10 measurements were obtained. In regard to the secondary effectiveness criterion, on average the AST declined by 3.7% and ALT declined by 4.3%, but these declines were not significant ($p = 0.374$ and 0.284 , respectively).

Significant declines of AST and ALT were observed in the phase II trial, but the nadir of the declines in these markers of hepatic inflammation was reached after 20 weeks [2]. In this trial, the AST and ALT were measured at week 8, which was 5.5 weeks after the fifth and last treatment. In the phase II trial, the nadir in the decline of AST and ALT was measured at 20 weeks following two periods of five treatments separated by 7-week “therapeutic holidays”. These data suggest that a greater time period than 4 weeks following treatment is required to achieve more significant declines in the AST and ALT. We speculate that more significant declines in both viral loads and AST and ALT would have resulted had the patients received 12 or more treatments in 8 weeks followed by testing at 10 weeks.

The mean reduction in log viral load and the number of patients with a reduction of log viral load of more than 0.49 was greater in the phase I trial (six of 9 patients after five treatments; seven of 10 patients by the end of the study) than in the phase II trial (three of 9 patients). This finding occurred even though the total number of treatments was greater in the phase II trial and is probably due to the amount of time without treatment in the phase II trial (“therapeutic holidays”) of 7 weeks between the first and the second and between the second and third treatment periods as described in Figure 1. During these “therapeutic holidays”, the virus could rebound without continuing therapeutic pressure.

While the experimental design appears similar between the phase I and phase II studies, there was a very important difference. The measurement of the viral load was performed within 3 days of the last UVBI treatment in the phase I study allowing little time for the remaining virus to replicate and increase. In contrast, in the phase II study, the measurement of the viral load was performed months after the last UVBI treatment thereby allowing much more time for the remaining virus to replicate, increase and rebound. The anecdotal cases reported in reference 2 show the possibility of reducing the HCV viral load to an undetectable level with continuous, periodic treatments uninterrupted by “therapeutic holidays.” Because of the differences observed in phase I and phase II studies, future studies of UVBI will be designed without therapeutic holidays and with target organism measurements immediately following the last UVBI treatment.

While UVBI is an effective therapy, its mechanism of action is only partially understood. Ultraviolet light in the B and C regions inactivates bacterial and viral DNA and RNA (Matsunaga, Hieda, & Nikaido, 1991; Miller, Plagemann, Davis, Rueckert, & Fleissner, 1974).

Lymphocytes and bacteria possess repair mechanisms for ultraviolet light-induced damage (Darwin & Nathan, 2005; Tuck, Smith, & Larcom, 2000). This ability of leukocytes to repair UV damage would appear to mitigate the risk of hematologic malignancy, and a large number of UVBI treatments (60,000) performed by 1948 without subsequent reports of cancer in the treated patients suggests that the procedure is safe (Miley & Christensen, 1948).

In order to explain the effect of UVBI, the predecessor company that initially developed the device used in this clinical trial (the HM), paid for investigative studies at the Louisiana State University (LSU). An in-vitro study of horse blood spiked with West Nile virus at a concentration of 3 logs was performed. Following treatment of the spiked blood samples with the modified Knott hemo-irradiator (HM), there was a 1.5 log reduction of the virus in subsequent viral cultures. This experiment showed that one of the mechanisms of UVBI efficacy is pathogen reduction.

Because approximately 4% of the circulatory blood volume is treated in any single UVBI session, possible mechanisms of immune stimulation by UVBI were also explored. In-vitro studies of the effect of the HM on the immune function of human leukocytes including lymphocytes, monocytes and

dendritic cells were conducted on behalf of the clinical trial sponsor. The essential findings of the study are quoted verbatim from the investigator's report.

“Observed increases in antigen presentation markers like MHCII and CD80 and CD86 were noted which may indicate a mechanism for induction of adaptive immunity induced by UV-radiation. The most interesting increases in surface marker expression were those belonging to the toll-like receptor families. Increases were seen in TLR4, which is strongly activated by LPS and reportedly mildly responsive to heat shock proteins. Interestingly, TLR2, the receptor responsible for recognition of gram-positive bacteria did not increase. Notably, levels of surface TLR3 were increased and a significant decrease was noted in intracellular TLR3. Toll-like receptor 3, which is normally sequestered intracellularly, recognizes double-stranded RNA, and is associated with viral infection. Signaling through this receptor induces the activation of NF- κ B and the production of type I interferons. Similarly, intracellular levels of TLR9 were decreased. TLR9 recognizes unmethylated CpG motifs and is localized internally, perhaps in lysosomal or endocytic compartments where it would more likely encounter its ligand. In summary, it appears that the innate immune response is significantly modulated after direct exposure to the UV wavelengths generated by the HM system.” (Unpublished research performed at LSU in June 2003 and June 2006). Additional possible mechanisms of action of UVBI are discussed in a case series report describing the resolution of Crohn's disease following treatment of infection by MAP (Kuenstner et al., 2015).

The limitations of this study include the small sample size of patients and the small number of treatments that were done on each patient. However, the limitations were set by the FDA in order for the study to proceed.

Considering the FDA Phase I and Phase II controlled clinical trials in patients infected with HCV (Kuenstner et al., 2015), two controlled clinical trials in tuberculosis (Shurygin, 2009; Zhadnov et al., 1995), and many case series reports for other infections (Hancock, 1942; Miley, 1943, 1944; Wasson et al., 1950; Rebbeck, 1942; Miley, 1942a, 1942b; Miley & Rebbeck, 1943; Rebbeck & Lewis, 1949; Miley & Christensen, 1948; Kuenstner et al., 2015), UVBI is a potential therapy for other infectious diseases that lack effective therapy (Kuenstner et al., 2017).

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Conflict of Interest

JTK and TP are shareholders of AVIcure Bioscience, LLC, which has a proprietary interest in the UVBI device and disposables used in this study. All other authors declare that they have no conflict of interest.

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