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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

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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

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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