UV-A1 Therapy for Nephrogenic Systemic Fibrosis

Kien T. Tran, MD, PhD; Heidi B. Prather, BS; Clay J. Cockerell, MD; Heidi Jacobe, MD

Background: Nephrogenic systemic fibrosis (NSF) is a rare sclerosing skin condition associated with end-stage renal disease and gadolinium exposure. Therapy for NSF is challenging, with few options other than preventing exposure to gadolinium and improving renal function through transplant. However, in some cases neither of these options is tenable. We report the successful use of UV-A1 phototherapy in 4 patients with NSF.

Observations: Four patients with NSF were treated with UV-A1 phototherapy at a tertiary medical center from 2005 through 2007. To our knowledge, it is unique to this series that all patients were receiving hemodialysis before, during, and after therapy with UV-A1. All experienced improvement in the degree of induration, and 2 experienced improvement in mobility of the hands and legs. Total treatments ranged from 22 treatments (with a cumulative dose of 1855 J/cm²) to 50 treatments (total UV-A1 exposure, 3850 J/cm²). No adverse events were observed.

Conclusions: Although no patient had complete resolution of indurated plaques, the improvement was substantial. For 2 patients, it resulted in a resumption of hand and leg mobility. As a result, UV-A1 therapy may represent a treatment for NSF when kidney transplantation is not an option or is delayed. Limitations of this study include the lack of a controlled trial, lack of quantification of gadolinium levels within tissue, and the lack of a defined grading scale for NSF severity.

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O R I G I N A L L Y D E S I G N A T E D nephrogenic fibrosing dermopathy, nephrogenic systemic fibrosis (NSF) is a rare, sclerosing skin condition that usually occurs in the setting of renal insufficiency, especially chronic kidney disease requiring hemodialysis. Exposure to gadolinium, especially the gadodiamide form, has been implicated in almost all cases of NSF. Lesions are initially usually edematous, erythematous plaques on the distal extremities. Over time, they develop a woody induration with a cobblestone appearance. Nephrogenic systemic fibrosis may rarely involve extracutaneous sites such as skeletal muscle, the diaphragm, and myocardium. Pruritus, pain, and burning accompany NSF, along with loss of joint mobility.

No definitive treatment for NSF exists. Because it is rare, the existing literature consists of case reports or case series. Currently, prevention of exposure to gadolinium in patients with renal impairment is considered ideal. Improvement in renal function is associated with involution of NSF lesions in some cases. Extracorporeal photopheresis (ECP) is another modality with some supporting evidence for efficacy. Case reports of treatments with varying success include imatinib mesylate, plasmapheresis, intravenous immunoglobin, topical steroids, topical calcipotriene, and oral immunosuppressants such as methotrexate. Other reported treatments include psoralen UV-A (PUVA) and photodynamic therapy. These modalities all have significant drawbacks, including their invasive nature, the cost of ECP, problems with polypharmacy, and immunosuppression in a population with clinically significant preexisting morbidity. Ultraviolet A1 phototherapy is attractive because it avoids these issues.

Ultraviolet light therapy in the long-wave UV-A range (340-400 nm) is a potentially viable treatment option for NSF because of its deep penetration into the dermis and superficial part of the subcutis. In addition, UV-A1 is used successfully in

Author Affiliations:
Department of Dermatology, University of Texas Southwestern Medical Center, Dallas.
other sclerosing skin conditions, including localized scleroderma, systemic sclerosis, and chronic sclerodermoid graft vs host disease. There is 1 prior case report of the successful use of UV-A1 phototherapy in NSF. However, the patient had transient renal compromise and did not require hemodialysis. This makes it difficult to determine if improvement was the result of normalization of renal function or UV-A1. Herein, we report the use of UV-A1 therapy to treat 4 patients with NSF. Unique to these cases is the chronicity of hemodialysis. All patients were undergoing hemodialysis prior to, during, and after treatment with UV-A1, with no notable change in renal function.

### RESULTS

**CASE 1**

Patient 1 was a 62-year-old white woman with a history of alpha-1-antitrypsin deficiency requiring a lung transplant in 1995 with renal insufficiency. She was admitted in 2006 for acute renal failure thought to be related to the toxic effects of tacrolimus. During this admission, she received a magnetic resonance imaging (MRI) scan with gadodiamide contrast for evaluation of altered mental status. Hemodialysis was started simultaneously. After 3 weeks, she developed erythematous, edematous plaques with some desquamation on her extensor and volar forearms, legs, thighs, and buttocks. She complained of pruritus and burning along with loss of range of motion in her ankles and hands. Findings from her biopsy specimen were consistent with clinically suspected NSF. Workup by a rheumatologist included an antinuclear antibody (ANA) profile and a double-stranded DNA profile. Findings from both tests were negative. She did not meet diagnostic criteria for scleroderma. After 2 months, UV-A1 therapy was instituted at 30 J/cm². At the time treatment was initiated, the patient had experienced progressively worsening induration of her extremities. She could weakly twitch her fingers but was unable to make a fist and had limited mobility at the knee and ankle, resulting in difficulty in walking. Within 10 treatments at a total dose of 505 J/cm², the patient noted a decrease in the sclerosis and edema of her arms and legs along with decreased pruritus and burning. After 50 treatments (total dose; 3850 J/cm²), she was gree of induration by palpation; and the progression of lesions before and after treatment.

### METHODS

From 2005 through 2007, 4 patients with NSF were evaluated at the University of Texas–Southwestern (UTSW) Medical Center in Dallas. All shared clinical and histologic features supporting the diagnosis of NSF along with a medical history of end-stage renal disease (ESRD) requiring hemodialysis. In all patients, hemodialysis protocols remained unaltered during and after treatment with UV-A1. Patient characteristics and outcome are outlined in the following case summaries and in the Table.

All patients were treated with a UV-A1 bed (Sellamed Systems, model 24000; Sellamed, Gevelsberg, Germany). Output for this device is 5 J/cm² per minute. Patients were treated 3 times per week beginning with a low to medium dose (30-60 J/cm²) increasing to a high dose (120 J/cm²) of UV-A1. The starting dose was determined by Fitzpatrick skin type. The dosage was increased by 10 J/cm² per visit as long as no erythema occurring dose was determined by Fitzpatrick skin type. The dosage A1, with no notable change in renal function.

### Table. Patient Summary

<table>
<thead>
<tr>
<th>Patient Profile</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause of kidney disease</strong></td>
<td>Tacrolimus toxic effects</td>
<td>Hypertension</td>
<td>Diabetic nephropathy</td>
<td>Hypertension</td>
</tr>
<tr>
<td><strong>Stage of kidney disease</strong></td>
<td>ESRD</td>
<td>ESRD</td>
<td>ESRD</td>
<td>ESRD</td>
</tr>
<tr>
<td><strong>Time to onset of NSF after gadolinium exposure</strong></td>
<td>3 wk</td>
<td>5 mo</td>
<td>Few months (unspecified)</td>
<td>Few months (unspecified)</td>
</tr>
<tr>
<td><strong>Duration of hemodialysis before NSF symptoms presented</strong></td>
<td>3 wk</td>
<td>2 mo</td>
<td>y</td>
<td>3 mo</td>
</tr>
<tr>
<td><strong>Time between initial symptoms and UV-A1 treatment</strong></td>
<td>2 mo</td>
<td>2 mo</td>
<td>y</td>
<td>3 mo</td>
</tr>
<tr>
<td><strong>Hemodialysis during and after UV-A1 treatment?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Renal transplant?</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>NSF proven by biopsy?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Type of gadolinium</strong></td>
<td>Gadodiamide</td>
<td>Gadodiamide</td>
<td>Gadopentate dimegumine</td>
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</tr>
<tr>
<td><strong>Fitzpatrick skin type</strong></td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Treatments until documented improvement, No. (total UV-A1 exposure, J/cm²)</strong></td>
<td>10 (505)</td>
<td>16 (1540)</td>
<td>32 (3140)</td>
<td>9 (700)</td>
</tr>
<tr>
<td><strong>Treatments, No. (total UV-A1 exposure until discontinuation, J/cm²)</strong></td>
<td>50 (3850)</td>
<td>16 (1540)</td>
<td>41 (4065)</td>
<td>22 (1855)</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ESRD, end-stage renal disease; NSF, nephrogenic systemic fibrosis.
able to nearly make a fist. She continued to experience induration of her legs, but her range of motion was improved, and progression of the disease had halted. Ultraviolet A1 therapy was discontinued, and the patient continued to receive physical therapy to increase the mobility in her hands. One year after UV-A1 therapy was discontinued, her condition remained stable, with no recurrence of disease activity. She was able to make a fist and experienced continued improvement in range of motion at the knee and ankle along with improved ambulation.

CASE 2

Patient 2 was a 72-year-old white woman with a history of hypertension resulting in ESRD who had been undergoing hemodialysis for 3 months prior to developing erythematous, tender plaques on her upper and lower extremities. The patient had received an MRI scan with gadodiamide contrast 5 months prior. On examination, her left arm and forearm had greater involvement than her right. Her calves had plaques covering the lateral and posterior surfaces. Her range of motion was intact in the upper and lower extremities. Findings from a biopsy were compatible with the clinical suspicion for NSF. Findings from a workup for scleroderma, including ANA, anti-scl70, and anticientromere antibody profiles, were negative. Previous treatment included triamcinolone acetonide cream without improvement, and actual progression of the lesions. Treatment with UV-A1 was started at a dose of 60 J/cm² 2 months after the onset of NSF. At follow-up after 16 treatments, the patient experienced notable improvement with decreased induration, and disease progression was halted. Ultraviolet A1 therapy was discontinued at the patient’s request owing to improvement and problems with travel. One year after discontinuing UV-A1 therapy, the patient maintained improvement without development of new lesions.

CASE 3

Patient 3 was a 57-year-old Hispanic woman with a history of diabetes mellitus, hypertension, and hepatitis C who had been undergoing long-term hemodialysis for ESRD secondary to diabetic nephropathy. She had an MRI scan with gadopentate dimeglumine, with onset of lesions shortly thereafter. She was initially treated with antibiotics for presumed cellulitis but had no other treatment. Her initial evaluation at UTSW Medical Center occurred 2 years after she had developed contiguous woody plaques on the upper and lower extremities, sparing the trunk. Her lesions impaired daily function with severe involvement of her popliteal fossa and ankles, resulting in an inability to walk and a very limited range of motion of the wrists and elbows. Biopsy findings, along with clinical presentation, were consistent with NSF. Therapy with UV-A1 was instituted at 60 J/cm². After 32 sessions, she was noted to have softening in the popliteal fossa with ability to extend the legs and improved mobility. The treatments were continued for 41 sessions (total dose, 4065 J/cm²). She also received physical therapy. After discontinuation of UV-A1, she did not have recurrence or progression of her NSF (remission) and had regained her ability to walk. This was maintained up to 6 months after discontinuation of UV-A1; thereafter the patient was lost to follow-up.

CASE 4

Patient 4 was a 71-year-old African American woman with a history of hypertension resulting in ESRD who had been undergoing hemodialysis for 3 months when she developed erythematous, tender plaques on the forearm of the left arm along with bilateral involvement of the posterior arms, thighs, and legs (Figure 1). The plaques occurred a few months after the patient underwent MRI with gadolinium contrast and, over time, developed woody induration. Biopsy findings were consistent with NSF (Figure 2). Ultraviolet A1 therapy was instituted at a dosage of 60 J/cm². Follow-up at treatment 9 (total dose, 1160 J/cm²) showed improvement in induration. At treat-
ment 22 (total dose, 3310 J/cm²), UV-A1 phototherapy was discontinued owing to considerable improvement in existing lesions and apparent remission of active disease. The improvement was maintained during 9 months of follow-up.

**COMMENT**

This case series comprised 4 patients with NSF who were treated successfully with UV-A1 therapy. All of the patients had exposure to gadolinium either concurrent with or before development of cutaneous signs suggestive of NSF. Patients had histologic evidence supporting NSF to verify the clinical findings. No patient developed signs of systemic involvement that would necessitate systemic treatment in place of or in addition to UV-A1 phototherapy. To our knowledge, it is unique to this case series that all patients were diagnosed as having ESRD and were receiving hemodialysis before, during, and after presentation with NSF. Cutaneous improvement did not occur until after institution of UV-A1 therapy. After UV-A1 therapy was discontinued, no patient had a relapse, nor did any patient have spontaneous continued improvement (patients were in remission).

Within our study, all patients had experienced improvement in induration with a decrease in pain and pruritus. For patients 1 and 3, the concomitant increase in joint mobility resulted in an enhanced quality of life that was the major therapeutic benefit of UV-A1 therapy. However, none had complete resolution of cutaneous findings. This might relate to premature discontinuation of therapy in some cases. All had difficulty maintaining tri-weekly appointment schedules in light of their ongoing hemodialysis. Another possibility might be the inability of UV-A1 to penetrate to the entire depth of the lesion.

The mechanism of action of UV-A1 in the treatment of NSF is unclear. In other sclerotic conditions, such as systemic sclerosis, there is an increase in type I and type III collagen. In scleroderma, UV-A1 radiation seems to increase synthesis of collagenase I in vitro and in vivo in fibroblasts. Along with this, UV irradiation inhibits procollagen synthesis in human skin. Kafi et al were able to demonstrate elevated procollagen I and III messenger RNA (mRNA) levels along with an increased mRNA level in the upstream signaling elements of transforming growth factor β and connective growth factor beta1 expression in affected skin. Twelve weeks of UV-A1 phototherapy resulted in a decrease in induration along with normalization of the mRNA levels of these cytokines and procollagen in the same report by Kafi et al. This would suggest that UV-A1 therapy alters the cytokine levels relating to fibrocytes to promote a less fibrotic environment. Also, initiation of UV-A1 early in the development of NSF is of greater benefit.

No therapy, including renal transplant, is totally effective in the treatment of NSF. In lieu of a renal transplant, ECP is currently the treatment option with the most support data. Although ECP is a well-tolerated procedure, it is more invasive than UV light therapy, requiring large-bore peripheral venous access or central venous access. Adverse effects from ECP include hypotension, flulike symptoms, and anemia. Extracorporeal photopheresis is also more costly than UV-A1. Psoralen–UV-A therapy has also shown promise in the treatment of NSF, but utilization of PUVA requires oral ingestion of psoralens and concomitant adverse effects. Furthermore, patients undergoing hemodialysis are routinely prescribed a polypharmacy regimen, which increases the risk of a drug-drug interaction. Ultraviolet-A1 phototherapy is noninvasive and does not require the use of systemic medications. One issue, however, is that currently UV-A1 therapy is not widely available in the United States.

Herein, we describe a series of 4 patients with NSF treated successfully with UV-A1 phototherapy. Unlike the prior case report by Kafi et al, the patients were all diagnosed as having ESRD and were undergoing hemodialysis during and after UV-A1 therapy with no change in their renal status during therapy. Although none had complete resolution, all had notable improvement, with 2 showing a return of joint mobility with considerable quality-of-life improvement. The earliest documented improvement for our series occurred within 3 weeks or 9 treatments, with peak improvement occurring after 41 to 50 treatments. Owing to the rapidity and ease with which phototherapy can be instituted, we advocate that UV-A1 phototherapy be considered a potential treatment option for patients with NSF where it is available. Although promising, our data are limited to a case series. One disadvantage in our case series is the lack of a scoring system, such as the Rodnan skin scoring system, for objectively measuring involvement before and after UV-A1 therapy. Furthermore, quantification of gadolinium with measurement of changes, if any, during therapy would be of interest in further ascertaining the potential mechanism of action of UV-A1 phototherapy in NSF. Finally, future investigations should include a controlled trial comparing the current treatment modalities.

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**Correspondence:** Heidi Jacobe, MD, Department of Dermatology, University of Texas–Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75390-9069 (heidi.jacobe@utsouthwestern.edu).

**Author Contributions:** Dr Jacobe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Tran and Jacobe. **Acquisition of data:** Tran and Prather. **Analysis and interpretation of data:** Tran, Cockerell, and Jacobe. **Drafting of the manuscript:** Tran, Prather, and Jacobe. **Critical revision of the manuscript for important intellectual content:** Tran and Jacobe. **Administrative, technical, and material support:** Cockerell and Jacobe. **Study supervision:** Jacobe. **Dermatopathology:** Cockerell and Tran.

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**REFERENCES**


