Photochemistry and Photobiology, 2012, 88: 1023–1026

Rapid Communication

Photodynamic Therapy Can Improve Warts' Discomfort in Renal Transplant Patients Prospective Multicenter Study

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Received 6 August 2011, accepted 7 February 2012, DOI: 10.1111/j.1751-1097.2012.01114.x

ABSTRACT

Many studies have been conducted showing that aminolevulinic acid (ALA)-photodynamic therapy (PDT) can be an alternative treatment for recalcitrant warts. Recently, we performed a study evaluating methyl-aminolevulinic acid (MAL)-PDT for the treatment of hand warts in a population of renal transplant patients. Two symmetrical targets were selected on each hand and randomly assigned to chemical keratolytic treatment followed by three cycles of ALA-PDT (75 J cm^{-2} red light). Patients were evaluated after 3 months and a second run of PDT was performed if the total area and number of warts decreased less than 50%, with evaluation every 3 months for 1 year. Twenty patients were included and 16 were evaluable (9 M, 7 F). After 6 months the reduction of warts' area was 48.4% on the treated side *versus* 18.4% in the control area ($P = 0.021$). The decrease in the total number of warts was 41% *versus* 19.4% (P = NS). The global tolerance of the treatment was good with acceptable pain during irradiation. These results suggest that ALA-PDT is a safe and efficient treatment for transplanted patient warts. The improvement between treated and control zone is 20% due to the decrease in untreated warts' area and number.

INTRODUCTION

Treatment of palmoplantar viral warts is usually painful, not very effective and mostly disappointing and frustrating for both patients and physicians (1). During the last years, many studies have been conducted showing that ALA (topical 5-aminolevulinic acid)-photodynamic therapy (PDT) can be an alternative treatment for recalcitrant warts (2). From 1990, it is well demonstrated that ALA can penetrate though disrupted epidermis and therefore can be an effective treatment for warts. The first pilot studies for the treatment of warts reported cure rate of 90–100% (3,4). Many reports have confirmed that ALA-PDT was able to destroy most warts after removal of hyperkeratotic regions that prevent a good penetration of ALA. Recently, comparative randomized studies have been performed using ALA and placebo creams before illumination (5). They have shown some control rates of 60–75% in the ALA-PDT groups compared with 25% in the placebo groups. Viral warts also frequently occur in transplant patients due to prolonged immunosuppression. The prevalence of viral warts increases with the duration of immunosuppression reaching 30–50% of patients after 5 years and also depends on the level of immunosuppression. Viral infection with human papilloma virus (HPV are responsible for common and plane warts and condylomata acuminata. Warts can occur on multiple localizations and are often associated with chronic sun exposed areas. Oncogenic HPV can explain the link between viral warts and cutaneous carcinomas. In organ transplant patients, common and plane warts are mainly recalcitrant and may affect the patient's quality of life. For these reasons, warts present a real therapeutic challenge in immunocompromised patients. Therefore, we conducted a comparative and randomized study evaluating MAL (methyl-aminolevulinic acid)-PDT for the treatment of hand warts in a population of renal transplant patients in three centers.

PATIENTS AND METHODS

Patients. Consecutive renal transplant patients with recalcitrant viral hand wart (excluding anogenital condylomas), referred to three Departments of Dermatology (Limoges, Caen and Grenoble) were considered eligible for this randomized study. Patients with stable immunosuppressive treatment for 3 months and with at least two warts on each target zone were eligible to participate in this study. Previous treatment and duration were not exclusive. Exclusion criteria were lack of informed consent, known hypersensitivity to methyl aminolevulinate physical or chemical destruction within 1 month before inclusion in the study, skin carcinomas in the target zone, acute graft rejection, porphyria, HIV and pregnancy.

Methods. After the signature of informed consent, two symmetrical targets (5 cm diameter) were selected on each hand or foot and randomly (right or left side) assigned to chemical keratolytic treatment (with 30% salicylic acid daily during 8 days) followed by one cycle with three sessions of MAL-PDT at 1 week intervals (Curelight^{TM}, with a fluence rate of 150 mW cm^{-2} for 15 mm, corresponding to a total dose of 75 J cm^{-2}, ranging in wavelength from 570 to

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670 nm, with a fluorescent red light source). All warts were numbered and were traced on template to calculate the area. The control target area received only the keratolytic treatment (8 days before). Two target zones were stripped with scalpel. On treated target area, topical application of MAL (Metvix® [Galderma, Watford, UK]; 160 mg g^{-1}) was performed under occlusive film dressings (Tegaderm® [3M, Cergy Pontoise, France] for 3 h). The cream was applied in thick layer (0.2 g cm^{-2}). Three hours later, all warts were illuminated with a red light source. Patients were evaluated after 3 months and a second run of PDT was performed if the total area and number of warts decreased less than 50%. Patients were evaluated every 3 months for 1 year. The main objective was to evaluate the efficacy of MAL-PDT for the treatment of warts in renal transplant patients. Secondary objectives were adverse events, tolerance and relapse rate of warts 6 months after treatment.

The primary end point was a 50% decrease of treated area compared with control area at 3 and 6 months after treatment. Investigators measured both treated and controlled areas with templates counted and photographed warts on each target zone. Pain was evaluated after each treatment by visual analog scale. Patients filled a questionnaire at 6 months to evaluate the modalities of PDT treatment. This protocol was approved by the ethical committee (CPP sud-ouest and outremer IV).

Statistical analyses. All data were analyzed with SAS Version 7 (SAS Institute Inc., Cary, NC). Univariate comparisons of categorical variables were performed. Wilcoxon rank-sum test was used to determine whether changes from baseline to follow-up were significant or not. $P < 0.05$ was considered significant.

RESULTS

The demographic characteristics

Twenty consecutive renal transplant patients with warts who fulfilled inclusion criteria and none of the exclusion criteria were included during 12 months and 16 were evaluable. Four patients were lost to follow-up (one death, one consent withdrawal, two lost to follow-up). All patients were referred from the departments of dermatology and nephrology of the three centers. Nine (56%) were men and 7 (44%) were women (9 male, 7 female). Mean age was 52.3 years (range: 41–62). The average transplantation time was 12.3 years (range: 4–24) and the median duration of warts at entry was 7.3 years (range: 5–10).

Entry characteristics of warts of two target zones, which were comparable, are summarized in Table 1. The average area was 105 mm^2 for the treated zone and 114 mm^2 for the control zone with an equivalent number of warts (14 *versus* 13). There was no significant difference between entrance areas in the two target zones ($P > 0.05$). All warts were localized on hand. Fourteen patients had hyperkeratotic warts and two patients had plane warts. Fourteen patients underwent prior treatments without efficacy.

The wart area decreased significantly in the MAL-PDT-treated warts

Six patients had one run of three sessions and 10 patients needed a second run after 3 months. After 6 months the reduction of warts' area was 48.4% on the treated side *versus* 18.4% in the control area ($P = 0.021$; Figs. 1 and 2). The wart area decreased significantly in the MAL-PDT-treated warts compared with the untreated side at month 6. Results are shown in Table 2. The decrease in the total number of warts was 41% *versus* 19.4% (P = NS; Table 2). The number of vanished warts was not significantly higher in the MAL-PDT compared with the untreated side.

Table 1. Characteristic of warts at entry enrolled in MAL and no treated hands.

Warts	Average area (mm^2)	Average number
PDT	105	14
Control	114	13

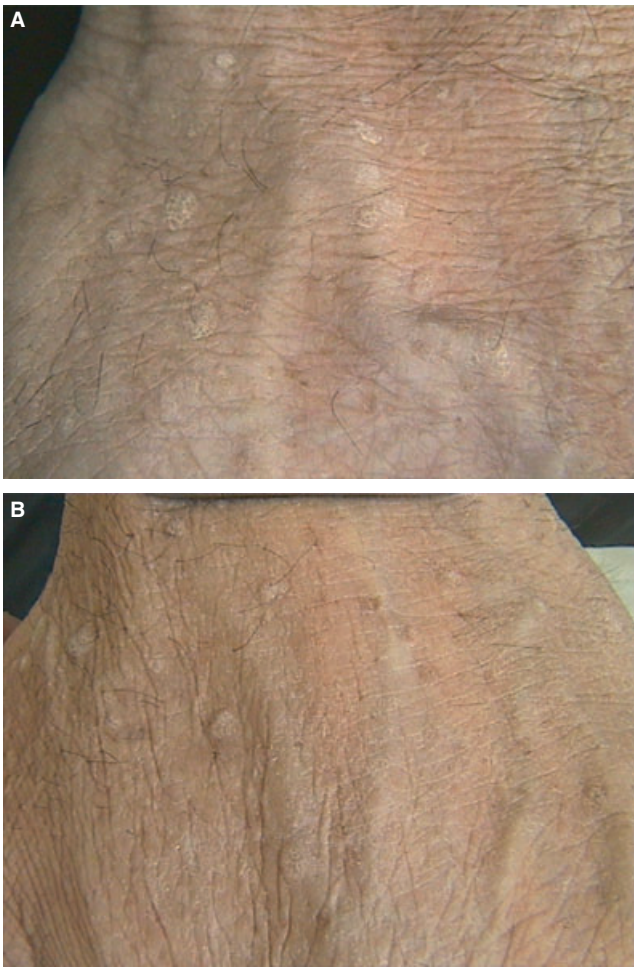

Figure 1. (A) Warts on right hand; (B) Warts on left hand before treatment.

Good compliance

Compliance with treatment was excellent. The global tolerance of the treatment was good with acceptable pain during irradiation (16/20 patients) and 14 of the 16 patients were satisfied with the treatment. One patient did not to continue because of excessive pain. Ten patients noted mean score of 1 with visual analog scale. For five patients, score was 3, 3, 4, 4 and 8 during light exposure. During and immediately after treatment, the pain intensity was significantly higher in treated side than in untreated side. Adverse events were crusting and persistent burning sensation. No systemic adverse events occurred in any patient.

DISCUSSION

These results suggest that MAL-PDT is a safe and efficient treatment of renal transplant patients. This study shows that

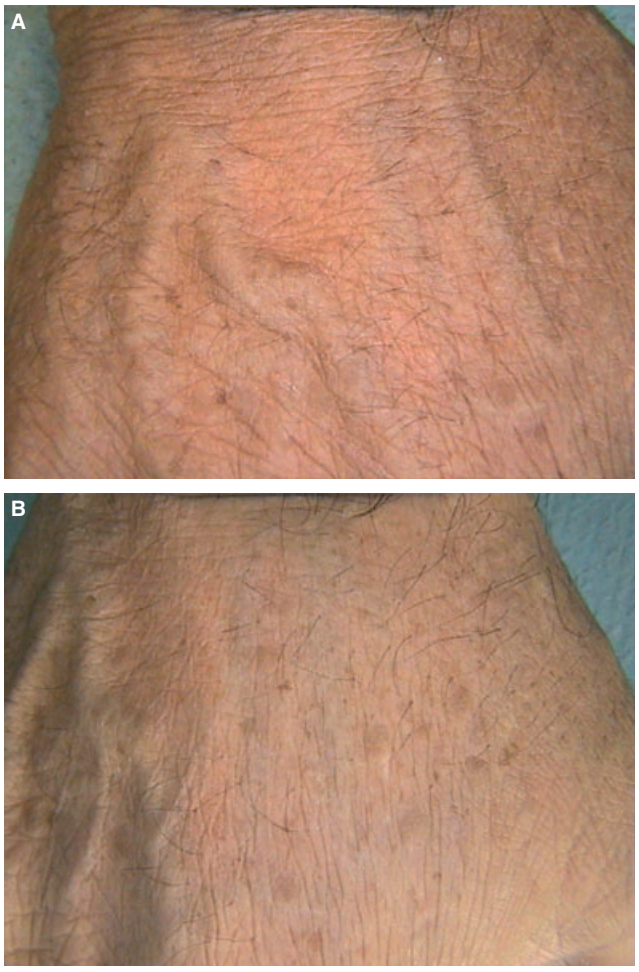

Figure 2. Result after three sessions of MAL-PDT. (A) Right hand and (B) Left hand.

Table 2. Relative change in wart area (%) and number of persisting warts compared with area at entry at months 3 and 6.

% Improvement	M0-M3	*P*	M3-M6	*P*	M0-M6	*P*
PDT	11.7	NS	41.5	**0.049**	48.4	**0.021**
Control	6.6		12.4		18.2	

$P < 0.05$.

MAL-PDT is better than keratolytic treatment in reducing area of recalcitrant hand warts in renal transplant patients, but not in reducing the number. The improvement between treated and control zone is 20% due to the decrease in untreated warts' area and numbers. There was no correlation with the decrease in terms of area or number. Our results confirm a significant decrease in warts' area, whereas the total number of warts is not statistically significantly lower in untreated areas. This is probably due to the small number of patients recruited in this study. This small number can be easily explained: at the time of the study PDT was not available in many dermatology departments and we needed to have the same procedure of illumination to reach concordant results. Moreover, it is always difficult in a population of immunocompromised patients to get stable disease and stable treatment three months before and during the entire study period. Patients had better acceptance of persisting warts. We observed a decrease of hyperkeratosis and thickness and skin softness improved. Patients did not relapse after 9 months.

For the first time, this study has used MAL-PDT as a single treatment of viral warts in renal transplant patients. One study used methyl-aminolevulinic acid to treat recalcitrant viral warts with another light source (like pulsed dye laser) and demonstrated complete clearance of their warts (6). Chong and Kang reported that recalcitrant viral wart on thumb had disappeared after three sessions of MAL-PDT (7). All other studies concluded that ALA-PDT is effective in treating viral warts (8–10). MAL is a valuable alternative photosensitizer to ALA as it is more lipophilic, has better penetration and probably causes less pain. Good clinical practice implies that therapeutical trials should be placebo controlled. During this study this was not possible for two main reasons: first of all manufacturing a placebo cream is expensive, secondly it is obvious that burning and pain occur at the very beginning of the illumination procedure and therefore does not allow a double blind evaluation.

Stender *et al.* reported a cure rate of 56% of warts treated with aminolevulinic acid photodynamic therapy compared with 42% treated by placebo photodynamic therapy (11). In their study, warts' area decreased more than total number of warts. Fabbrocini *et al.* showed that 75% of ALA-PDT treated warts had resolved and so had 23% of control warts (10). Smucler and Jatsova noted that 100% of warts in 24 patients were cured by ALA-PDT with pulsed dye laser source (12). In another study, 88% of plantar viral warts showed a complete response (13).

We have selected a population of renal transplant patient. Warts are usually seen in immunocompromised patients. First warts occur after 1 year of transplantation and increase with time of transplantation to reach 30–50% after 5 years. HPV infection in immunocompromised patients is common and can induce cancers. Ciclosporine is widely used to avoid graft rejection and may also promote cancer progression by transforming growth factor beta. The combination of UV radiation, HPV infection and immunosuppressive drugs is a strong argument to develop alternative treatments in this population. There is no reference treatment in immunosuppressed patients. Granel-Brocard *et al.* reported the efficacy of ALA-PDT in a recalcitrant wart in an immunodeficient patient (14).

Verruca planae on the hands were present in two patients in our study. These two patients achieved complete response. Thickness is important and explains that fewer sessions are needed to obtain good results and a better penetration of photosensitizer (15).

In our study, the number of sessions was six in the majority of the patients (10/16). This was due to the thickness of warts presented by our patients (hyperkeratosis verrucae vulgares) (6).

Despite the small difference in terms of number of warts cured by PDT, most patients claimed that PDT had clearly improved their skin condition and general comfort. This was due to the decrease of warts' areas and hyperkeratosis. PDT also improves collagenous synthesis and therefore, skin softness for a long period of time.

No serious local or systemic adverse events occurred in any patients during or after MAL-PDT. The most frequent adverse event reported during ALA-PDT is pain (16). Pain was tolerable in our study for the majority of patients. Wang *et al*. noted mild to moderate pain lasting no longer than 48 h and was well tolerated by all patients (17).

These findings suggest that PDT is probably capable of inducing an additional immunological effect. MAL-PDT is not a first line treatment. This alternative treatment could be proposed to patients with multiple viral warts.

Acknowledgements—The authors are grateful to Mrs. Hilde Morris from Photocure SA (Norway) for providing the MAL cream used in this trial.

REFERENCES

1. Gibbs, S. and I. Harvey (2006) Topical treatments for cutaneous warts. *Cochrane Database Syst. Rev*. **3**, CD001781.
2. Smetana, Z., Z. Malik, A. Orenstein, E. Mendelson and E. Ben-Hur (1997) Treatment of viral infections with 5-aminolevulinic acid and light. *Lasers Surg. Med*. **21**, 351–358.
3. Peng, Q., T. Warloe, K. Berg, J. Moan, M. Kongshaug, K. E. Giercksky and J. M. Nesland (1997) 5-Aminolevulinic acid-based photodynamic therapy. Clinical research and future challenges. *Cancer* **79**, 2282–2308.
4. Fritsch, C., G. Goerz and T. Ruzicka (1998) Photodynamic therapy in dermatology. *Arch. Dermatol*. **134**, 207–214.
5. Stender, I. M., J. Lock-Andersen and H. C. Wulf (1999) Recalcitrant hand and foot warts successfully treated with photodynamic therapy with topical 5-aminolaevulinic acid: a pilot study. *Clin. Exp. Dermatol*. **24**, 154–159.
6. Fernandez-Guarino, M., A. Harto and P. Jaen (2010) Treatment of recalcitrant viral warts with pulsed dye laser MAL-PDT. *J. Dermatolog. Treat*. **22**, 226–228.
7. Chong, W. S. and G. Y. Kang (2009) Dramatic clearance of a recalcitrant acral viral wart using methyl aminolevulinate-red light photodynamic therapy. *Photodermatol. Photoimmunol. Photomed*. **25**, 225–226.
8. Stahl, D., N. K. Veien and H. C. Wulf (1979) Photodynamic inactivation of virus warts: a controlled clinical trial. *Clin. Exp. Dermatol*. **4**, 81–85.
9. Bastuji-Garin, S., R. Laurent, N. Basset-Seguin, C. Bédane, P. Combemale and L. Dubertret (2001) Traitement photodynamique avec acide 5-Aminolévulonique ou placebo pour les verrues des pieds et des mains: essai randomisé en double aveugle. *Ann. Dermatol. Venereol*. **128**, 1110–1113.
10. Fabbrocini, G., M. P. Di Costanzo, A. M. Riccardo, M. Quarto, A. Colasanti, G. Roberti and G. Monfrecola (2001) Photodynamic therapy with topical delta-aminolaevulinic acid for the treatment of plantar warts. *J. Photochem. Photobiol., B* **61**, 30–34.
11. Stender, I. M., R. Na, H. Fogh, C. Gluud and H. C. Wulf (2000) Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomised double-blind trial. *Lancet* **355**, 963–966.
12. Smucler, R. and E. Jatsova (2005) Comparative study of aminolevulic acid photodynamic therapy plus pulsed dye laser *versus* pulsed dye laser alone in treatment of viral warts. *Photomed. Laser Surg*. **23**, 202–205.
13. Schroeter, C. A., J. Pleunis, C. van Nispen tot Pannerden, T. Reineke and H. A. Neumann (2005) Photodynamic therapy: new treatment for therapy-resistant plantar warts. *Dermatol. Surg*. **31**, 71–75.
14. Granel-Brocard, F., J. F. Cuny and J. L. Schmutz (2008) Efficacy of photodynamic therapy (PDT) in a recalcitrant wart in an immunodeficient subject. *Eur. J. Dermatol*. **18**, 601.
15. Lu, Y. G., J. J. Wu, Y. He, H. Z. Yang and Y. D. Yang (2010) Efficacy of topical aminolevulinic acid photodynamic therapy for the treatment of verruca planae. *Photomed. Laser Surg*. **28**, 561–563.
16. Stender, I. M., F. M. Borgbjerg, J. Villumsen, J. Lock-Andersen and H. C. Wulf (2006) Pain induced by photodynamic therapy of warts. *Photodermatol. Photoimmunol. Photomed*. **22**, 304–309.
17. Wang, Y. S., Y. K. Tay, C. Kwok and E. Tan (2007) Photodynamic therapy with 20% aminolevulinic acid for the treatment of recalcitrant viral warts in an Asian population. *Int. J. Dermatol*. **46**, 1180–1184.