Potential use of Microwave Technology in Dermatology

A. K. Gupta^{1,2}, M. Venkataraman², L.T. Joshi³, E.A. Cooper²

¹ Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
² Mediprobe Research Inc., London, Ontario, Canada
³ School of Biomedical Science, University of Plymouth, Plymouth PL4 8AA, UK
ORCID#: AKG (<u>https://orcid.org/0000-0002-8664-7723</u>)
LTJ (<u>https://orcid.org/0000-0002-5965-4055</u>)

Corresponding author:

Aditya K. Gupta 645 Windermere Road London, Ontario, Canada N5X 2P1 Phone: 519-851-9715 Fax: 519-657-4233 Email: agupta@mediproberesearch.com

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ABSTRACT

Background: Microwaves are electromagnetic radiations used in medicine for diagnostics and treatment of cancers and other infectious diseases. Recently, novel microwave devices (Swift®, Emblation Ltd, UK and miraDry, Miramar Labs Inc, CA) have been cleared by the FDA and Health Canada for various dermatological conditions.

Objective and Methods: To comprehensively analyze the literature on the use of microwavebased treatments for plantar warts, actinic keratosis, axillary hyperhidrosis, osmidrosis, hidradenitis suppurativa, and dermatophyte infections. Clinical trials, case reports, or *in vitro* studies for each condition are summarized.

Results and Conclusion: Microwaves are a promising alternative therapy for cutaneous warts, actinic keratosis, axillary hyperhidrosis, and osmidrosis, along with a favorable safety profile. However, patients with hidradenitis suppurativa have had negative clinical outcomes. A preliminary *in vitro* study indicated that microwave ablation treatment inhibited the growth of *T. rubrum*. We also present the first human case of toenail onychomycosis successfully treated with microwaves. Despite the advancements in the use of microwaves, the knowledge behind the mechanisms and their impact is limited. Further research and the conduct of high-quality randomized, well-conducted, clinical trials with larger patient groups and long follow-up periods are required to evaluate the clinical benefits and possible adverse effects of microwaves in treating dermatological conditions.

1. INTRODUCTION

Microwaves are a part of the electromagnetic spectrum (**Figure 1**), widely used in industries, such as food processing, communications, medical research, and biosensor diagnostics. The wavelengths range from 1 metre to 1 millimetre in free space, and frequencies range from 300 MHz to 300 GHz (1). Microwaves were developed for communication and satellite navigation in the 1950s, utilizing their electromagnetic wave properties. Microwaves were used in domestic appliances in the late 1970s to reduce the microorganisms in food through targeted thermal deactivation or killing. The Industrial Scientific and Medical (ISM)-approved frequency range for domestic purposes is 2.45 GHz (2).

Since the early 1980s, microwaves have been utilized in medicine (**Figure 2**) to visualize a tumor (e.g. breast cancer) or treat cancer and other microbial infections, or to transmit wireless data from an implanted medical device (e.g., pacemaker) to an external device (data telemetry) (3). In diagnostics, microwave detections are based on the electrical properties of the tissue. Typically, microwave therapeutic applications depend on their thermal effect. The range of frequencies available with microwave technology makes it ideal for a range of medical applications (4). Treatments using higher frequencies, such as 5.8 GHz - 10 GHz, lead to shallow penetration of energy and, therefore, are ideal for surface-based cosmetic treatments or conditions that require precise ablation procedures (5).

Herein, we report the first case of using microwaves to treat toenail onychomycosis in humans. The patient (**Figure 3**) had a toenail dermatophytoma which was particularly difficult to treat with oral or topical antifungal therapy. Microwave therapy successfully treated dermatophytoma in this patient. Furthermore, we summarize the current literature regarding the mechanism of action, current and prospective use of microwaves as a therapeutic modality across dermatological conditions (**Figure 4**).

2. DERMATOLOGICAL CONDITIONS IN WHICH MICROWAVES HAVE BEEN EVALUATED

2.1 CUTANEOUS WARTS

The clinical appearance of warts may vary depending on the type of HPV and the anatomical site (6,7). There are about 150 different forms of HPV, with HPV types 1, 2, 4, 27, or 57 causing the majority of vertuca vulgaris lesions (8).

The most common topical preparation used is salicylic acid (SA) (8). Other topical agents include 5-fluorouracil, podophyllin, and silver nitrate (6). Cryotherapy with liquid nitrogen can be considered if topical treatments have been ineffective or contraindicated. Additionally, it can be an adjunct to topical therapy. Cryotherapy causes tissue destruction; in a meta-analysis of RCTs, this therapy had low efficacy to manage common warts (with a mean clearance on all sites of 49%) (9).

The common treatment endpoint is the clinical cure, defined as the complete disappearance of elevated/warty skin (6). Warts that relapse or are resistant to primary treatment may be treated with systemic immunotherapy, targeting the viral life cycle, or surgical excision of the infected skin (6). Even with an armamentarium of treatments available, warts remain a persistent problem.

Microwaves are a new treatment modality introduced in North America in January 2019 for plantar warts. Swift® is a novel microwave device that is FDA-cleared, Health Canada approved, and CE marked.

2.1.1 Mechanism of action and treatment protocol

For plantar warts, a typical treatment consists of a 7 mm diameter microwave applicator (handheld device) that emits 8-10W (watts) of microwave energy directly to the affected area. An average treatment session involves 3-5 applications, each lasting 2 seconds, spaced one second apart (10) and 3-4 sessions each a month apart.

This microwave device uses a specialized probe to deliver low-dose microwave energy to the underlying HPV virus in the skin, thereby successfully treating it by boosting the natural immune response. Microwave application on the skin works on dielectric heating. Microwave energy applied to the infected tissue at a depth of 2 to 4 mm, heats the tissue cells from around 42°C to 45°C. The heat is created by the agitation of the polar water molecules, which collide, causing localized heating (10,11). This heating of the infected tissue triggers an immunological

response driven by heat shock proteins (HSP), allowing the body to detect and eliminate the HPV virus. Subsequently, the infected tissue is repaired, replaced, and regenerated through apoptosis.

On-going research has observed the response to localized topical microwave energy in HPV16 positive cervical tumour cells of 3D organotypic raft cultures. Although oncogenic in HPV type and of different tissue types, it demonstrates some principles that may underlie external dermatology applications. This *in vitro* work shows inhibited cell proliferation (Ki67); activated apoptosis (caspase 3) and autophagy (LC3B); increase of heat shock proteins (HSP70), and translational stress (G3BP and PABP) in cervical cancer tissues (12).

Any topical or cooling agent should not be applied directly to the skin after microwave treatment. Complete resolution may be achieved depending on the patient's immune response (10). Clinicians report that even in the case of diabetic patients, those with compromised or suppressed immune systems, the efficacy is not greatly impaired.

2.1.2 Clinical evidence

Bristow et al. (13) evaluated the efficacy of locally delivered microwaves in treating cutaneous viral warts in an uncontrolled phase I study (**Table 1**) (13–15). The study design, patient characteristics, treatment regimen, clinical endpoint, and adverse events of patients with warts and corns treated with microwaves are listed in **Table 1** (13-15). This study reported that 75.9% of recalcitrant plantar warts resolved, with an average of 3 treatment sessions. The study also observed activation of dendritic cells (CD80, CD86, CD40) and enhancement of anti-HPV responses by CD8+ T cells induced by microwave-treated keratinocytes (13).

Post-marketing surveillance of this therapy in the UK, based on an online survey, reported that the efficacy rates were 79.2% (65.9 - 87.5%) for plantar and 82.3% (71.4 - 100%) for common warts. There was complete resolution of warts with three treatments on average. On a 10-point scale, patients were "very satisfied" (16).

2.1.3 Adverse events

For a typical 5-second treatment, patients generally reported moderate discomfort for about 2 seconds, which subsided after the treatment. There was also a common observation that discomfort decreased with subsequent treatments (13). The lesions were described as painful and

assessed using a numerical scale (scored out of 10). There were significant reductions in pain immediately following the first session (13). Feedback from early post-market surveillance found a shortened treatment time of 2 seconds would be used without compromising on efficacy. Further post-marketing surveillance of this lower dose microwave treatment in the UK reported a few adverse events, including blistering, superficial ulceration, and delayed healing (n=7), based on an online 79-item survey (16). Even though there is limited evidence, this microwave technology could be an effective and safe treatment for cutaneous warts.

The microwave energy vibrates water molecules, generates friction, and does not damage DNA. The microwaves do not break the skin, thus lowering the risk of infection (10). Moreover, the device delivers less energy into the skin than typical laser and electrocautery treatments (17) which typically involve vaporization, destruction and necrosis of the tissue. There is no risk of lateral spread/damage with microwaves, as they penetrate to a pre-determined depth into the targeted area.

2.1.4 Benefits of microwave therapy compared to conventional treatments for cutaneous warts

Sterilization of the applicator tips is not required, since a new one's used for each patient (10). As a result of the short microwave treatment time (2-5 seconds), this technology offers clinical advantages over current wart treatments such as cryotherapy and electrosurgery. In contrast to ablative lasers and electro-surgery, microwave treatment does not produce vapor or smoke, eliminating the need for air extraction systems to contain the spread of viral particles (18).

Besides a light debridement, no pre-treatment preparation or anaesthesia is generally not required. The non-invasive nature of the procedure requires no post-treatment dressing (10). Although this procedure involves some pain, patients generally do not experience pain after the procedure (10).

2.2 ACTINIC KERATOSIS

Actinic keratosis (AK) is a premalignant skin condition that can progress to cutaneous squamous cell carcinoma (cSCC) (19). Cryotherapy is widely used to treat AKs. Topical agents include 5-fluorouracil and imiquimod. Other treatments with devices include laser and photodynamic therapy (20). Many AK therapies necessitate weeks of dedicated application that may cause

severe inflammation. Furthermore, many AK patients are in the older cohort, and a lesiondirected treatment would make compliance easier (21,22).

2.2.1 Microwave treatment protocol

The Swift® ablation device is used for the treatment of AKs. The applicator delivers microwave energy to the skin at a diameter up to 6 mm and a depth of 2–6 mm depending on the treatment protocol (11).

2.2.2 Clinical evidence

Jackson et al. investigated the feasibility and efficacy of microwaves to treat AKs on the forehead, bald scalp, and dorsal hand (19). This was the first-in-human two-stage study on microwave therapy for AK. The first stage used specialist instrumentation to determine the dielectric properties of the lesion(s) thus deriving an optimized dose for the microwave device to deliver targeted non-ablative energy (below 50°C) (23). The second stage was the randomized, controlled trial evaluating the safety and efficacy of the optimized microwave treatment in resolving AK.

Patients with a minimum of six AK lesions on both the right and left sides of the forehead/scalp/dorsal hand were included in the study. The dielectric properties of the lesion (n=7 patients), such as the relative permittivity, conductivity, and loss tangent, were measured in stage I. These measurements were used to compute the energy required to raise the tissue temperature into the non-ablative range (23). Thus, the optimized computed microwave treatment was calculated as 5W for 3 seconds and repeated delivery three times with a 20-seconds gap.

In Stage II, patients (n=11 patients) were randomized to receive treatment (n=93 AKs) on one side of the forehead/scalp/dorsal hand, and the other side was the untreated control (n=86 AKs) (19). The applicator was placed in the centre of the lesion for each delivery. Lesions larger than the probe were also treated to evaluate the effectiveness of this treatment. However, this energy caused a lot of discomfort, pain, and scabbing in patients (n=2), thus suggesting that the energy range could be in the ablative region. Based on the modelling information the study protocol was amended to use 4W for 3 seconds for hyperkeratotic 'thick' (Olsen scale grade 3) and 3W for 3 seconds for nonhyperkeratotic 'thin' (grade 1 or 2) lesions. Around 10/11 patients

underwent a second treatment session after 28 days. Patients were followed up at 1, 2, 4, 6, 8and 16-weeks post-treatment.

A significantly larger proportion of treated AKs (78% at day 8 and 90% at day 120 posttreatment) resolved partially or completely with microwave therapy compared to untreated control AKs (2% at day 8 and 15% at day 120 post-treatment) (p<0.001) (19). Lesions larger than the applicator tip showed complete resolution of the area under the tip, but there was some persisting AK outside of this treatment area, hence these lesions were reported as a partial response. Thin lesions exhibited a higher response rate than thick lesions (p<0.001). During treatment, the majority of individuals felt 'moderate' or 'severe' pain, and after 30 minutes, all participants reported no pain (19). Microwave therapy appears to be a potential treatment for AK, with 90% resolution of lesions at 120 days post-treatment.

2.2.3 Adverse events

Adverse events were mild, such as erythema (n= 6 patients), flaking (n=3 patients), and itch (n=3 patients) (19).

2.2.4 Benefits of microwave therapy compared to conventional treatments for actinic keratosis

Microwaves could be a potential lesion-directed therapy used in a physicians office. It is important to assess the advantages and disadvantages of each available therapeutic option and patient adherence.

2.3 FUNGUS

Treatment of dermatophyte infections primarily involves oral and/or topical formulations of azoles or allylamines, particularly itraconazole and terbinafine. Topical medications applied once or twice daily for 12 months are the primary treatment for tinea corporis/cruris and tinea pedis/manuum. Sometimes oral/topical antifungals are not effective, and there are increasing reports of dermatophyte resistance, particularly to terbinafine therapy (24–26).

2.3.1 In vitro data

Budihardja et al. investigated the effect of microwave radiation on dermatophyte-infected (*Trichophyton rubrum, T. rubrum var. nigricans, T. interdigitale* and *Microsporum canis*) cork

and polyethylene sponge shoe insoles (27). The microwave used for this experiment was a 2450 MHz microwave oven (SHARP type R-24W, 800 W).

In polyethylene sponge insoles, there was complete growth inhibition of *T. rubrum* when irradiated at 240W for 20 seconds, *T. rubrum var. nigricans* at 240W for 40 seconds, *M. canis* at 240W for 70 seconds, and *T. interdigitale* at 560W for 30 seconds. Similarly, in cork insoles, there was complete growth inhibition of *T. rubrum* when irradiated at 240W for 30 seconds, *T. rubrum var. nigricans* at 240W for 40 seconds, *M. canis* at 240W for 50 seconds. The maximum temperature reached was 35°C, 50°C, 50°C, and 60°C for *T. rubrum, T. rubrum var. nigricans, M. canis*, and *T. interdigitale*, respectively. To achieve complete growth inhibition in *T. interdigitale*, higher intensities and longer irradiation durations were required (27).

Earlier studies of microwave irradiation of micro-organisms (e.g., *E. coli*, *Staphylococcus aureus)* utilized the thermal effects (28,29). However, disinfection of shoes may involve the non-thermal effect of microwaves (27). This microwave irradiation requires only a short duration, protects the material, and has no adverse effect on the skin, as the insoles remained undamaged, validating the non-thermal effect of microwaves (27).

Microwave treatment has been explored as an alternative for toenail fungal infection. In a preliminary *in vitro* study conducted by Emblation Ltd, the effects of a range of continuous and pulsed microwave exposures were examined on cultures of *T. rubrum* for 10 days on agar and 72 hours in liquid broth [*Unpublished data, Emblation Ltd*]. The microwave applicator was applied to the bottom of the petri dish vertically from outside to mimic the nail plate and skin. The doses delivered were specific to *in vitro* use only. The following settings were tested: (1) H-50 (50°C): 15W for 20 seconds followed by 5W for 30 seconds (2) M-44 (44°C): 15W for 13 seconds followed by 5W for 20 seconds (3) L-41 (41°C): 20W for 10 seconds followed by 5W for 20 seconds (4) pulsed dose P-50 (50°C): 20W for 3 seconds repeated 3 times followed by 20W for 5 seconds repeated 3 times. Halos of inhibition were measured on the agar each day after microwave ablation, and inhibition of growth in the liquid broth was examined. Inhibition was clear and optimal for regimens P-50 (mean area of clearance 87.625 mm²) and H-50 (mean area of clearance 46.75 mm²) for *T. rubrum* in agar plates. Similar results were seen in liquid broth with H-50 (least optical density after 50 hours; however, there was no complete growth

inhibition). H50 (50°C) regimen was optimal for inhibition of *T. rubrum* in agar and broth. This study indicates that sustained 8GHz microwave ablation treatment can inhibit the growth of *T. rubrum*.

2.3.2 Preliminary in vivo evidence

The microwave regimen recommended by Emblation Ltd. successfully treated a patient with a toenail dermatophytoma, diagnosed using the diafactory dermatophyte immunochromatographic method. The causative agents include *T. rubrum, T. mentagrophytes* [*var. interdigitale*], *T. violaceum, T. tonsurans, Microsporum gypseum, M. canis,* and *E. floccosum*. The patient received 7-9W of energy for 3 seconds, repeated 3 times in each location of the infected area. The nails were pretreated by soaking in warm water for 5 minutes. The patient received a total of 6 treatments with an interval of 6-32 weeks between each treatment session. **Figure 3** shows the successful response of the patient to microwave therapy. The preliminary data shows evidence of the efficacy of the microwave treatment for onychomycosis.

2.4 AXILLARY HYPERHIDROSIS

Axillary hyperhidrosis (or excessive underarm sweating) is a prevalent condition that affects 1.4% of the US population (30). The major cause of this condition could be the overstimulation of the eccrine sweat glands. Axillary hyperhidrosis can be a significant burden, impairing personal interactions, emotional well-being, and self-esteem. Lifestyle and behavioral recommendations are part of the initial treatment. Antiperspirants such as aluminium chloride, iontophoresis, laser treatment, botox injections, and endoscopic thoracic sympathectomy are among the current treatments (31). Botox may be an effective treatment with minimal side effects. However, the procedure warrants a qualified clinician to administer injections (32). Although laser treatment is effective, there may be adverse effects such as hyperpigmentation, hypopigmentation, erythema, edema, pain, blistering, and scarring (33,34).

Due to their non-invasive nature, microwave-based devices are becoming more popular for the treatment of axillary hyperhidrosis. The miraDry microwave device was US FDA cleared in 2011 and is CE-marked in Europe to treat axillary hyperhidrosis (35). It's currently available in more than 50 countries around the world. It was subsequently cleared by the FDA in 2015 for the permanent removal of underarm hair and odor glands (osmidrosis) (35). The miraDry System MD4000 is now indicated for the treatment of primary axillary hyperhidrosis and unwanted and permanent axillary hair loss in all colors of Fitzpatrick skin types I-IV (35,36).

2.4.1 Mechanism of action and treatment protocol

This device consists of an integrated vacuum and cooling system (DTS G2 System; Miramar Labs, Sunnyvale, CA, USA) (37). A handheld device delivers precisely controlled electromagnetic energy to the axillary sweat glands resulting in heat-induced thermolysis of sweat glands; however, the superficial layers of the skin are simultaneously cooled and protected. Through suction, the device brings the sweat glands closer to the surface and the energy selectively heats the water-rich dermis and sweat glands using microwaves. After treatment, the sweat glands are not expected to regenerate, so the effects are noticeable almost immediately and last a long time. Despite eccrine glands being the primary target, microwave devices can also affect odor-producing apocrine glands, thus used in the treatment of osmidrosis (excess or foul odor) (38). This device has a microwave output frequency of 5.8 GHz and energy level settings ranging from 1 to 5, corresponding with a delivery time in seconds between 2.4 and 3.0 seconds (32). The number of treatments required depends on the sweat intensity of the patient. Typically, it is recommended that patients undergo two treatments 3 months apart (occasionally, a third treatment is needed) (35).

The treatment typically consists of 3 steps: 1. The treatment area (uni- or bilateral axillae) is identified through several methods (e.g., starch-iodine tests) and marked; 2. The marked treatment area is administered with local anesthesia to numb the region for a pain-free session; 3. The microwave device delivers targeted microwaves into the skin to eliminate sweat glands through thermolysis.

Specifically, Miradry operates at 5GHz and penetrates deeper than 8GHz (Swift®). The former seeks ablative therapy, leading to tissue necrosis, whereas the latter maintains sublative to stimulate an immune response and create an apoptosis route to healing.

2.4.2 Clinical evidence

The severity of axillary hyperhidrosis is generally assessed using a subjective measure such as the Hyperhidrosis Disease Severity Scale/Score (HDSS) (**Table 2**) (38–40). Other objective outcomes evaluated include gravimetric (weight) reading (41). The treatment area (axillae) is

wiped with a preweighed gauze or cotton pad for 1-5 mins. Then the pad is weighed again and the difference is calculated per axillae (41). **Table 3** (38–40,42–46) describes the clinical studies and case reports investigating the use of microwave treatment for axillary hyperhidrosis and osmidrosis.

2.4.3 Adverse events

Underarm swelling, redness, and tenderness are common and minor side effects of therapy (38–40). Patients may experience transient effects such as numbress or tingling sensation in the upper arm or armpit for about 5-weeks, which eventually resolves with time (38–40).

2.4.4 Benefits of microwave therapy compared to conventional treatment for hyperhidrosis

For hyperhidrosis, microwave therapy may offer a non-invasive, tolerable, and potentially permanent solution. Clinical studies have shown that, on average, the microwave treatment can reduce sweat and odor by 82% and 89%, respectively. The results may be long-lasting or even permanent (35).

2.5 HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa (HS) is an inflammatory disorder marked by recurrent painful erythematous nodules that usually appear in the axilla or inguinal region (47). Patients experience a significant psychological and functional burden because of the painful lesions (47). Treatments include topical therapy (e.g. clindamycin), systemic medications (e.g. tetracycline), biological agents, surgery, and light-based therapies, with mixed outcomes (48). Immunomodulatory treatments such as tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) inhibitors, and selective phosphodiesterase-4 inhibitors are among the more recent therapy options (PDE-4) (49). The only biologic approved by the US Food and Drug Administration (FDA) for moderate-to-severe HS is adalimumab (48). The clinical endpoints pertain to pain severity (based on visual analogue scale (VAS)), clinical response (based on hidradenitis suppurativa clinical response score (HiSCR)), quality of life (based on Dermatology Life Quality Index (DLQI)), and abscess count (50).

2.5.1 Microwave treatment protocol

MiraDry (Miramar Labs Incorporated, Santa Clara, CA) microwave device is a potential treatment for targeting HS lesions, due to thermolysis of hair follicles, eccrine, and apocrine glands in the (hypo)dermis through the heat generated by the microwaves (39,51).

2.5.2 Clinical evidence

Vossen et al. investigated the efficacy and safety of this microwave treatment for mild axillary HS in a randomized intrapatient-controlled trial with 9 mild HS patients, each with a total of 3-5 abscesses or nodules (AN) per axilla with less than one abscess or draining sinus (Trial registered at https://www.clinicaltrials.gov (identifier NCT03238469)) (51). Patients received a single microwave session (5.8 GHz, energy level 5, manufacturer-recommended settings) of one axilla (other axilla acted as control), following the administration of tumescent anesthesia, and followed up for 3 months. The primary outcome measure was to compare the axillary areas from left to the right using the HiSCR. The definition of responders was: (i) reduction in ANs, (ii) no increase in the number of abscesses, and (iii) no increase in the number of draining fistulas from baseline (identifier NCT03238469). Secondary outcomes assessed include pain score per axilla, treatment satisfaction, and hair follicle count (average number of hair-containing follicles in 3 fields of 1 cm² assessed by dermoscopy).

The authors hypothesized that ablative therapy could improve the clinical symptoms of HS by lowering the number of hair follicles and reducing the inflammatory infiltrate and have a long-term effect due to the permanent removal of hairs and sweat glands (51). However, the interim analysis observed negative clinical results.

The nonselective targeting of the dermal zone, instead of a specific structure, may have contributed to the unsatisfactory trial results. While microwaves can eliminate HS lesions, the treatment triggers an intense inflammatory response that extends beyond the initially diagnosed lesions.

2.5.3 Adverse events

The study reported a serious adverse event, where one patient developed cellulitis of the upper arm, requiring antibiotic treatment (51).

2.5.4 Benefits of microwave therapy compared to conventional treatments for Hidradenitis Suppurativa

The risks have outweighed the benefits, and clinicians feel that microwaves cause more harm in HS patients (51). Based on similar reports from other clinics, the value of microwave ablative therapy for HS needs to be seriously evaluated.

2.6 FUTURE OF MICROWAVE-BASED THERAPY IN DERMATOLOGY

Although microwave treatment provides a new therapeutic option with favorable effects for patients suffering from different dermatological conditions, it is necessary to weigh the benefits against the risks. It is shown to be effective for cutaneous warts, actinic keratosis, and axillary hyperhidrosis. However, patients with hidradenitis suppurativa had their symptoms worsened with microwaves, and the trial was terminated. The utility of microwave ablative or non-ablative therapy needs to be understood in greater depth. Preliminary *in vitro* studies suggest that microwaves may be effective for treating fungal infections; furthermore, we have reported the first human case of onychomycosis to be effectively treated using microwave therapy. Further studies are in progress to evaluate microwaves for managing onychomycosis and condyloma acuminatum (anogenital warts) where the lesions share an HPV origin.

Thus, randomized, well-conducted, high-quality clinical trials with larger patient groups and long follow-up periods are required to evaluate the clinical benefits of microwaves in treating dermatological conditions.

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Figure legends

Figure 1. Electromagnetic spectrum

Figure 2. Applications of microwaves in medicine

Figure 3. Successful treatment of a patient with dermatophytoma using Swift® microwave therapy

Figure 4. Microwaves in dermatology