

Transepidermal drug delivery: a new treatment option for areata alopecia?

Maria Cláudia Almeida Issa, Marianna Tavares Fernandes Pires, Priscilla Sarlos Silveira, Esther Oliveira Xavier de Brito, Cristiane Cassab Sasajima

doi: 10.3109/14764172.2014.967778

Abstract

Background: Transepidermal drug delivery (TED) is a new potential method in dermatology. Permeability alterations induced by ablative fractional resurfacing have been described with the aim to increasing the delivery of different substances into the skin. **Objective:** To evaluate clinical response and side effects of TED in areata alopecia (AA) treatment using ablative fractional methods associated with acoustic pressure ultrasound (US) to deliver triamcinolone solution into the skin. **Methods and Materials:** Five cases of AA underwent treatment which comprised of 3 steps: 1) Ablative fractioned RF or CO2 laser 2) topical application of triamcinolone 3) acoustic pressure wave US. The number of sessions varied according to the clinical response, ranging from one to six sessions. **Results:** All patients had complete recovery of the area treated. Two of them treated with ablative fractional RF + triamcinolone + US had complete response after three and six sessions. The other two treated with ablative fractional CO2 + triamcinolone + US had complete response after one session. **Conclusion:** Fractioned ablative resurfacing associated with acoustic pressure wave US is a new option to areata alopecia treatment with good clinical result and low incidence of side effects.

© 2014 Informa UK, Ltd. This provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

DISCLAIMER: The ideas and opinions expressed in the journal's *Just Accepted* articles do not necessarily reflect those of Informa Healthcare (the Publisher), the Editors or the journal. The Publisher does not assume any responsibility for any injury and/or damage to persons or property arising from or related to any use of the material contained in these articles. The reader is advised to check the appropriate medical literature and the product information currently provided by the manufacturer of each drug to be administered to verify the dosages, the method and duration of administration, and contraindications. It is the responsibility of the treating physician or other health care professional, relying on his or her independent experience and knowledge of the patient, to determine drug dosages and the best treatment for the patient. *Just Accepted* articles have undergone full scientific review but none of the additional editorial preparation, such as copyediting, typesetting, and proofreading, as have articles published in the traditional manner. There may, therefore, be errors in *Just Accepted* articles that will be corrected in the final print and final online version of the article. Any use of the *Just Accepted* articles is subject to the express understanding that the papers have not yet gone through the full quality control process prior to publication.

Transepidermal drug delivery: a new treatment option for areata alopecia?

Maria Cláudia Almeida Issa, Marianna Tavares Fernandes Pires, Priscilla Sarlos Silveira, Esther Oliveira Xavier de Brito, Cristiane Cassab Sasajima

Hospital Universitário Antonio Pedro (HUAP) - Universidade Federal Fluminense (UFF), Dermatology, Niterói, Brazil

Correspondence: Dr. Marianna Tavares Fernandes Pires MD, Hospital Universitário Antonio Pedro - UFF, Dermatology, Av. Marques de Paraná, 303, Centro, Niterói, Niterói, 24030-210 Brazil, Email: marianna.pires@gmail.com

Short title: Transepidermal drug delivery in areata alopecia

Abstract

Background: Transepidermal drug delivery (TED) is a new potential method in dermatology. Permeability alterations induced by ablative fractional resurfacing have been described with the aim to increasing the delivery of different substances into the skin. Objective: To evaluate clinical response and side effects of TED in areata alopecia (AA) treatment using ablative fractional methods associated with acoustic pressure ultrasound (US) to deliver triamcinolone solution into the skin. Methods and Materials: Five cases of AA underwent treatment which comprised of 3 steps: 1) Ablative fractioned RF or CO₂ laser 2) topical application of triamcinolone 3) acoustic pressure wave US. The number of sessions varied according to the clinical response, ranging from one to six sessions. Results: All patients had complete recovery of the area treated. Two of them treated with ablative fractional RF + triamcinolone + US had complete response after three and six sessions. The other two treated with ablative fractional CO₂ + triamcinolone + US had complete response after one session. Conclusion: Fractioned ablative resurfacing associated with acoustic pressure wave US is a new option to areata alopecia treatment with good clinical result and low incidence of side effects. Key words: transdermal administration, alopecia, radiofrequency, ultrasound, CO₂ laser

Keywords: transdermal administration, alopecia, radiofrequency, CO₂ laser

INTRODUCTION

The stratum corneum acts as a barrier that limits the penetration of substances through the skin^{1, 2}. Low-frequency ultrasound (US) and, more recently, microneedle array^{3, 4} have been described to improve skin permeability. The use of fractional ablative methods with lasers^{5, 6} has been described with the aim to creating micro-channels in the epidermis to increase permeability of drugs topically applied.

Alopecia areata (AA) is the most common cause of non-scarring alopecia. It is suspected to be an autoimmune disease with a genetic predisposition. Environmental and ethnic factors seem to be involved⁷. Steroids are widely used to treat AA and intralesional triamcinolone is a very effective method⁸.

In this study we reported five cases of areata alopecia treated with ablative fractional resurfacing associated with acoustic pressure wave US. This procedure included three steps: 1- micro-channels were created in the epidermis through an ablative method: radiofrequency (RF) or CO₂ laser. 2- triamcinolone was topically applied on the perforated skin. 3- US was applied over the steroids to push this drug into the dermis through the pre-formed micro-channels.

METHODS

A prospective study was carried out to evaluate the clinical efficacy of applying steroids through transepidermal delivery by skin resurfacing associated with US in five patients with AA. To produce micro channels in the epidermis we used two different techniques (ablative RF and fractional CO₂ laser). The same steroid and the same US were applied on the skin after both ablative techniques (RF and CO₂).

The sessions were done every 3 weeks until we could observe clinical improvement on the patch, ranging from 1 to 6 sessions. All patients were submitted to dermatologic exam every month during the first 6 months, and were recruited to a final exam 12 months after the last session. They were advised not to use any other treatment during the study.

The degree of clinical improvement was evaluated according to a quartile scale of improvement as following: no improvement; 1-25%- minimal improvement; 26-50%- moderate improvement; 51-75%-marked improvement; 76-100% - excellent improvement⁹. Side effects such as pain and atrophy were evaluated on a 3-point scale (0= absent, 1= mild, 2= moderate, 3=severe). Digital photographs (Sony DSC-H9 – Super Steady Short 8.1 MP) were taken at baseline and at each follow-up visit to document clinical response.

TECHNIQUES

- *RF* technique

The ablative fractional RF used was unipolar RF with a roller tip. The RF roller is 10 mm width wheel comprised of 6 cogs/discs that has 50 pins lined on each cog's exterior rim. The 6 pins from each cog discharge micro-plasma causing perforation of the skin layer (holes of 100-150 µm in depth and 80-120 µm in diameter).

- CO₂ laser technique

The roller tip of the fractional CO₂ laser slides on the skin surface, producing micro-channels (pixels). It triggers a short-duration pulse of fractionated light via special beam splitter lens with fixed gaps between each 7x1 pixel. It produces microscopic holes of 150-300 µm in depth and 125-150 µm in diameter.

- Impact US technique

The acoustic pressure module is comprised of a transducer, a sonotrode and a distal hollow. The distal surface of the horn creates vibrational cycles ("push-pull") on the triamcinolone. The mode of operation is based on mechanical pressure and torques by propagation of US wave (frequency: 27kHz), creating a hammering-like effect in the thin layer between the triamcinolone, the skin and the sonotrode.

PROCEDURE

Before each session, the area to be treated was cleaned with aqueous chlorhexidine. At first, ablative fractional RF or CO₂ was applied to promote fractionated ablation of the skin with the following parameters: RF roller tip with 45 watts and 4 passes (crossed); and CO₂ roller tip with 60 W, 60 mJ/pixel, spacing 1 mm, 2 passes (crossed). After this step, the medication (triamcinolone acetonide - 20 mg/ml) was dropped (0,1 ml/1 cm²) on the skin surface pretreated by RF or CO₂. The last step was the US: 50 Hz (frequency of shocks) with 80% of impact intensity for one minute each 1 x 1 cm grid (Fig.1).

PATIENTS

Patient 1: A 23 year old man with an occipital patchy AA for 3 months was treated with fractional RF + triamcinolone + US - three sessions.

Patient 2: An 18 year old woman with multiple patches of AA on the parietal area for 12 years. All the patches were treated with fractional RF + triamcinolone + US - six sessions.

Patient 3: A 47 year old woman with an occipital patchy for one month was treated with CO₂ laser + triamcinolone + US - one session.

Patient 4: A 38 year old woman with one parietal patchy for three months was treated with CO₂ laser + triamcinolone + US - one session.

Patient 5: A 35 year old woman with AA for 12 years. Three patches were treated. One occipital patchy was treated with CO₂ laser + triamcinolone + US – one session. Another occipital patchy and one retroauricular patchy were treated with one session of different procedures as following: the occipital patchy was treated with CO₂ laser + triamcinolone, but without US; and the retroauricular patchy was treated with CO₂ laser isolated without triamcinolone or US. These lesions were treated with different protocols with the aim to having lesions control.

RESULTS

In all cases patients had an excellent improvement and only one patient (patient 2) didn't sustained the result after 12 months of follow up. Patient 1 who was treated with ablative fractional RF + triamcinolone + US had a

complete recovery of the patchy after three sessions, and the result was maintained after 12 months (Fig. 2). Patient 2 was submitted to six sessions of ablative fractional RF + triamcinolone + US to achieve a complete response, and sustained the result for 3 months when had an infectious respiratory disease. The three patients treated with pixel CO₂ + triamcinolone + US (patients 3, 4 and 5) clinical improvement could be observed in the first month just after one session of treatment, maintaining the result after 12 months (Fig. 3). On the other hand, as patient 5 had two other patches treated with different procedures, she had different clinical responses. The complete clinical response could only be observed in the patchy treated with the complete procedure (CO₂ + triamcinolone +US). We could observe a minimal clinical improvement in the occipital patchy after fractional ablation (CO₂ laser) + triamcinolone without US (Fig. 4a1, 4a2), and any response was observed on the retro-auricular patchy treated with fractional ablation (CO₂ laser) isolated (Fig. 4b1, 4b2).

None of the patients had atrophy in the treated area. They reported mild burning sensation during the procedure.

DISCUSSION

A number of treatments can induce hair growth in alopecia areata, and has been reported in literature, such as topical, systemic and intralesional corticosteroid injections⁸, topical immunotherapy¹⁰, photochemotherapy (PUVA)¹¹, minoxidil¹² and dithranol¹³. The use of fractioned resurfacing to create micro-channels in the epidermis to improve drug delivery into skin is a new concept of treatment called transepidermal drug delivery (TED) and have been reported in literature. Gómez *et al.*⁵ reported that Erbium laser ablation of stratum corneum enhances transepidermal delivery of 5-fluorouracil. Another paper published by Haerdersdal *et al.*⁶ evaluated drug delivery by CO₂ laser ablative fractional resurfacing using methyl 5-aminolevulinate. A new study about PDT after fractional ablative RF associated with impact US was reported in literature with good clinical results in actinic keratosis treatment even with methyl aminolevulinate incubation time reduced to one hour¹⁴. In 2012, the use of ablative fractional RF and acoustic pressure US associated with retinoic acid 0.05% cream was described as a safe and effective method for alba-type SD treatment¹⁵. More recently, we reported some cases of transepidermal triamcinolone acetate delivery using the same technique in hypertrophic scars treatment as a new possibility of treatment with high efficacy and low side effects¹⁶.

In this study we used two different technologies to promote ablative fractional skin resurfacing, ablative fractional RF and ablative fractional CO₂ both of them were associated with an acoustic pressure wave (impact US) which acted as a hammer to push the triamcinolone into the epidermis through the micro-channels pre-formed by RF and by CO₂ with the aim at increasing triamcinolone acetate permeability in areata alopecia patches.

It seems that with this new technique triamcinolone is applied more homogeneously on the skin comparing to needle injection, facilitating the treatment. Our lesions control showed the importance of the complete procedure, using an ablative method + triamcinolone + impact US.

CONCLUSION

TED using ablative fractional RF and CO₂ in association with high pressure acoustic wave US to deliver triamcinolone acetonide promoted an excellent clinical result in few sessions with low side effects in AA treatment. This new method of TED was effective and avoided the pain and skin atrophy caused by needle intradermal injection of triamcinolone.

References

- Curdy C, kalia YN, Guy RH. Non-invasive assessment of the effects of iontophoresis on human skin in-vivo. *The Journal of pharmacy and pharmacology* 2001 Jun; 53 (6): 769-77.
- Mori K, Hasegawa T, Sato S, et al. Effect of electric field on the enhanced skin permeation of drugs by electroporation. *Journal of controlled release: official journal of the Controlled Release Society* 2003 Jun 24; 90 (2): 171-9.
- McAllister DV, Allen MG, Prausnitz MR. Microfabricated microneedles for gene and drug delivery. *Annual review of biomedical engineering* 2000; 2: 289-313.
- Henry S, McAllister DV, Allen MG, et al. Microfabricated microneedles: a novel approach to transdermal drug delivery. *Journal of pharmaceutical sciences* 1998 Aug; 87(8): 922-5.
- Gómez C, Costela A, García-Moreno I, et al. Laser treatments on skin enhancing and controlling transdermal delivery of 5-fluorouracil. *Lasers in surgery and medicine* 2008 Jan; 40(1): 1-12.
- Haerdersdal M, Sakamoto FH, Farinelli WA, et al. Fractional CO₂ laser-assisted drug delivery. *Lasers in surgery and medicine* 2010 Feb; 42(2): 113-22.
- Al-Mutairi N, Eldin ON. Clinical profile and impact on quality of life: Seven years experience with patients of alopecia areata. *Indian journal of dermatology venereology and leprology* 2011 Jul-Aug; 77(4): 489-93.
- Chang KH, Rojhirunsakool S, Goldberg LJ. Treatment of severe alopecia areata with intralesional steroid injections. *Journal of drugs in dermatology* 2009 Oct; 8(10): 909-12.
- Walgrave SE; Ortiz AE; MacFalls MT, et al. Evaluation of a Novel Fractional Resurfacing Device for Treatment of Acne Scarring. *Lasers in surgery and medicine* 2009 Feb; 41(2): 122-7.
- Wiseman MC, Shapiro J, MacDonald N, et al. Predictive model for immunotherapy of alopecia areata with diphencyprone. *Archives of dermatology* 2001 Aug; 137(8): 1063-8.
- Taylor CR, Hawk JL. PUVA treatment of alopecia areata partialis, totalis and universalis: audit of 10 years' experience at St John's Institute of Dermatology. *The British journal of dermatology* 1995 Dec; 133(6): 914-8.

Fenton DA, Wilkinson JD. Topical minoxidil in the treatment of alopecia areata. British medical journal (Clinical research ed) 1983 Oct 8; 287(6398): 1015-7.

Fiedler-Weiss VC, Buys CM. Evaluation of anthralin in the treatment of alopecia areata. Archives of dermatology 1987 Nov; 123(11): 1491-3.

Kassuga LEBP, Issa MCA, Chevrand NS. Aplicação transepidérmica de medicamento associado a terapia fotodinâmica no tratamento de ceratoses actínicas. Surgical and Cosmetic Dermatology 2012; 4(1): 89-92.

Issa, MCA, Kassuga LEBP, Chevrand NS, et al. Transepidermal retinoic acid delivery using ablative fractional radiofrequency associated with acoustic pressure ultrasound for stretch marks treatment. Lasers in surgery and medicine 2013; 45: 81–88.

Issa MCA, Kassuga LEBP, Chevrand NS, et al. Topical delivery of triamcinolone via skin pretreated with ablative radiofrequency: a new method in hypertrophic scar treatment. International journal of dermatology 2013 Mar; 52(3): 367-70.

JUST ACCEPT

Figure Legends

Figure 1. TED procedure with fractional ablative CO₂. First step, applying the CO₂ roller tip; Second step, dropping triamcinolone acetonide on the perforated skin; Third step, applying the acoustic pressure US in areata alopecia patchy.

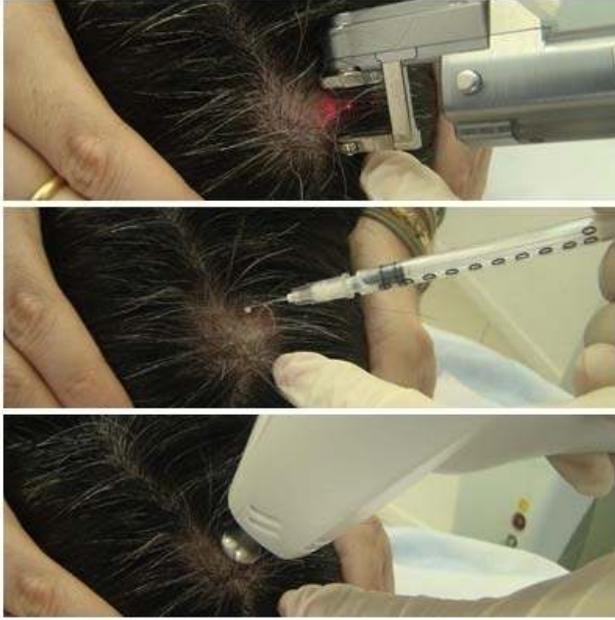
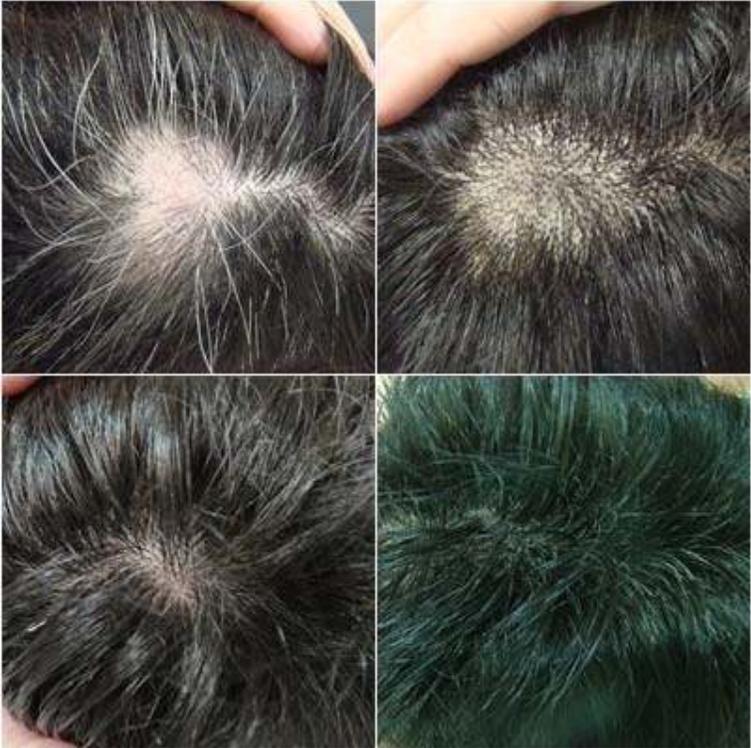


Figure 2. Gradual Improvement in the patchy of areata alopecia before, after 2 and after 3 sessions of RF + triamcinolone + US, and after 12 months of treatment.



Figure 3. Before, 3 weeks, 3 months and 12 months after treatment, one session of CO2 + triamcinolone + US.



JUST ACCEPTED

Figure 4. 4 a1, 4 a2: Occipital area: before and 3 months after CO2 laser + triamcinolone without US.

4 b1, 4 b2: Retro-auricular area: before and 3 months after CO2 laser isolated without triamcinolone or US.



JUST ACCEPTED