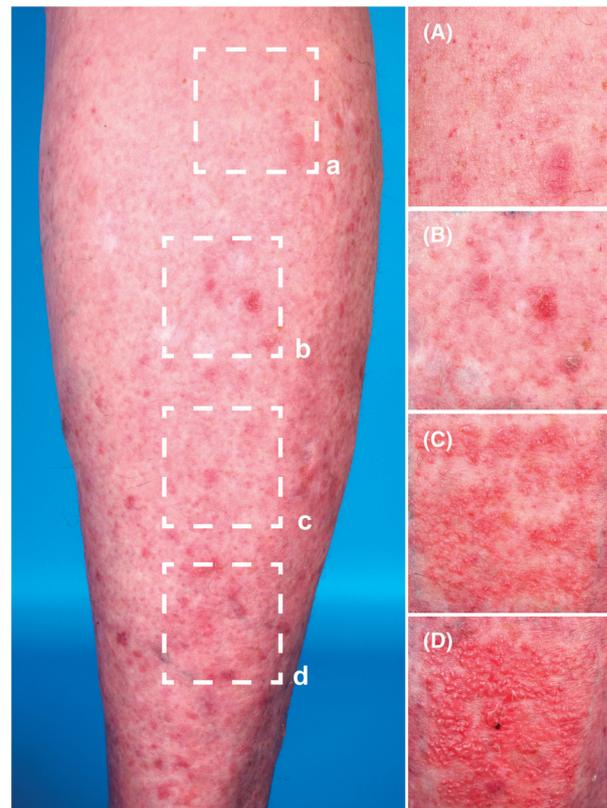


## Needling-Assisted Drug Delivery: Enhanced Response to Ingenol Mebutate After Microneedling

Recent studies have shown that pretreatment of the skin with ablative fractional lasers, followed by photodynamic therapy (PDT), is a safe and effective technique to increase the bioavailability of topically applied methyl aminolevulinate, leading to an improved clearance rate of actinic keratosis (AK).<sup>1,2</sup> Recently, Bencini and colleagues<sup>3</sup> and Torezan and colleagues<sup>4</sup> have shown that microneedling-assisted drug delivery (MADD) may also be an effective way to increase the efficacy of PDT. Following up on these concepts, our group has proposed that the benefits of laser-assisted drug delivery for the treatment of actinic field cancerization are not limited to PDT, but can also be applied to other drugs for the topical treatment of AK.<sup>5</sup> Ingenol mebutate (IM) is a first-in-class macrocyclic diterpene ester, extracted and purified from the plant *Euphorbia peplus*, which is effective for field treatment of nonhyperkeratotic AK.

Here, we report the application of MADD to IM therapy of a 59-year-old female patient with actinic field cancerization. Four test fields ( $3 \times 3 \text{ cm}^2$ ) were defined on the left lower leg and treated, from cranial to caudal, with: (1) microneedling (MyM Dermapen; Bomtech Electronics Co., LTD, Seoul, South Korea; depth: 0.5 mm, one pass) (Figure 1A), (2) IM-0.05%-gel (Figure 1B), (3) microneedling and consecutive application of IM-0.05%-gel (Figure 1C), and (4) IM-0.05%-gel and consecutive microneedling (Figure 1D). The next day, only minimal pinpoint bleeding was apparent after microneedling alone (Figure 1A) and a very discrete inflammatory reaction was observed in the field treated with IM-0.05%-gel alone (Figure 1B). In comparison, both combination therapies resulted in increased inflammation with readily apparent erythema and formation of small vesicles (Figure 1C, D), with microneedling following application of IM-gel inducing the most intense inflammatory reaction of the 4 test fields. All inflammatory reactions healed within 2 weeks with a good cosmetic outcome and, significantly, a partial response for the combination treatments as compared to no response for the treatment with either microneedling or IM-gel alone. The patient did not report on any systemic side effects.

These findings support earlier reports describing an increase in drug efficacy in the treatment of AK after pretreatment with MADD. An increase in efficacy potentially widens the indication spectrum of IM to the treatment of thicker lesions or lesions in areas (e.g., extremities) that may show recalcitrance to conventional field therapy. Yet, it must be noted that IM is only approved for topical use and that up to date no safety data are available regarding a potential needling-induced systemic absorption of IM.



**Figure 1.** A 59-year-old woman with actinic field cancerization on her left lower leg. The left panel shows the 4 defined test fields before treatment: (a) microneedling (MyM Dermapen, Bomtech Electronics Co., LTD, Seoul, South Korea; depth: 0.5 mm, one pass), (b) IM-0.05%-gel, (c) microneedling and consecutive application of IM-0.05%-gel, and (d) IM-0.05%-gel with consecutive microneedling. The right panels, (A) to (D), show the test fields at Day 1 after treatment: (A) minimal pinpoint bleedings after microneedling, (B) mild inflammatory reaction after IM-0.05%-gel, (C) modest inflammatory reaction with erythema and small vesicles after microneedling IM, and (D) marked inflammatory reaction with erythema and vesicles after IM microneedling. IM, ingenol mebutate.

In conclusion, these results indicate that IM can effectively be combined with microneedling and pave the way for expanded studies to determine the extent of enhancement of the efficacy and address safety of MADD-IM in the management of actinic field cancerization.

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STEPHAN A. BRAUN

PETER A. GERBER

*Department of Dermatology*

*Heinrich-Heine University*

*Düsseldorf, Germany*

PETER A. HEVEZI

*Department of Pediatrics*

*University of California*

*San Diego, California*

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S.A. Braun and P.A. Gerber have served as investigators and consultants for LEO Pharma and have received research funding and travel support. S.A. Braun has received honoraria for participating in advisory boards for LEO Pharma.

## Less Pain, More Gain: Lip Augmentation With Insulin Syringes

Lip fullness and definition are crucial aesthetic traits that define the attractiveness and youth of the lower face. Sensory nerves are highly concentrated in the lips, making filler injection very painful sometimes refraining patients from undergoing the procedure.<sup>1</sup>

In addition, the relatively large size of the cannulas and proprietary filler needles can cause postoperative edema and bruising.<sup>2</sup> Lip augmentation is a very delicate procedure that requires injection of small volumes of hyaluronic acid in the vermilion border and in the lip body. Accurate estimation of the amount injected can be difficult resulting in asymmetrical lips.<sup>3</sup> Insulin syringes have been previously used for filler injection with good cosmetic results and a favorable safety profile.<sup>2</sup>

Our technique consists of injecting Juvéderm Volbella with Lidocaine (Allergan, Santa Barbara, CA) using 8-mm insulin syringes with 30-gauge needles without any topical anesthesia. Under aseptic conditions, the filler product is decanted into insulin syringes. Each

syringe can comfortably accommodate up to 0.2 mL of filler material. On a sterile dressing pack, the plunger of the insulin syringe is removed and the proprietary filler with the manufacturer needle is inserted in the back of the insulin syringe; 0.2 mL is injected in the rear end. The plunger is then reinserted, pushing the material to the tip of the insulin syringe.

The product is delivered by bolus injections of 0.02 mL per central point of injection and 0.01 mL per lateral point of injection. Injections are made at 2 to 3 points per side per lip (Figure 1). The small boluses and the precise injection points produce very symmetrical lips, without any palpable lumps (Figures 2–5). The product is delivered in the superficial dermis. Similarly, injections are made using the same volume in the lip body at the “wet-dry” line. The procedure is followed by gentle massage of the lips.

An additional advantage of using insulin syringes is the reduction of pain and discomfort during the procedure.