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The International Academy of Cosmetic Dermatology
The Section on Dermatology College of Physicians of Philadelphia
The History of Dermatology Society
International Association of Ecological Dermatology (Eco-Derm)
Philippine Academy of Clinical and Cosmetic Dermatology
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INDICATION AND USAGE

Taclonex® Topical Suspension is indicated for the topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older and for plaque psoriasis of the scalp in patients 12 to 17 years. Patients 18 years and older should not use more than 100 g per week and patients 12 to 17 years should not use more than 60 g per week.

IMPORTANT SAFETY INFORMATION

Taclonex® Topical Suspension is not for oral, ophthalmic, or intravaginal use and should not be applied to the face, axillae, or groin. Do not use if atrophy is present at the treatment site. Do not use with occlusive dressings unless directed by a physician.

If hypercalcemia or hypercalciuria develop, discontinue until parameters of calcium metabolism normalize. Taclonex® can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent steroid. Cushing's syndrome and hyperglycemia may also occur in adults. Pediatric patients are at a greater risk than adults of systemic toxicity, HPA axis suppression and adrenal insufficiency.

The most common adverse reactions (≥1%) are folliculitis and burning sensation of skin.

Patients who apply Taclonex® to exposed skin should avoid excessive exposure to either natural or artificial sunlight. There are no adequate and well-controlled studies of Taclonex® Topical Suspension in pregnant women. Safety and effectiveness of the use of Taclonex® Topical Suspension in pediatric patients under the age of 12 years have not been established.

Please see Brief Summary of Prescribing Information on the following page.

References: 1. Taclonex® Topical Suspension [package insert]. Parsippany, NJ: LEO Pharma Inc.; August 2014. **2.** Segaert S, Ropke M. The biological rationale for use of vitamin D analogs in combination with corticosteroids for the topical treatment of plaque psoriasis. *J Drugs Dermatol.* 2013;12(8):e129-e137.

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BRIEF SUMMARY (See Package Insert for full Prescribing Information).

INDICATIONS AND USAGE: Taclonex® Topical Suspension is indicated for the topical treatment of:

- Plaque psoriasis of the scalp and body in patients 18 years and older
- Plaque psoriasis of the scalp in patients 12 to 17 years

WARNINGS AND PRECAUTIONS: Hypercalcemia and Hypercalciuria: Hypercalcemia and hypercalciuria have been observed with use of Taclonex® Topical Suspension. If hypercalcemia or hypercalciuria develop, discontinue treatment until parameters of calcium metabolism have normalized. The incidence of hypercalcemia and hypercalciuria following Taclonex® Topical Suspension treatment of more than 8 weeks has not been evaluated. **Effects on Endocrine System:** Taclonex® Topical Suspension can cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of treatment. Factors that predispose a patient to HPA axis suppression include the use of high-potency steroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age. Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test. In a trial evaluating the effects of Taclonex® Topical Suspension and Taclonex® Ointment on the HPA axis, 32 adult subjects were treated with both Taclonex® Topical Suspension on the scalp and Taclonex® Ointment on the body. Adrenal suppression was identified in 5 of 32 subjects (16%) after 4 weeks of treatment and in 2 of 11 subjects (18%) who continued treatment for 8 weeks. In another trial of 43 subjects treated with Taclonex® Topical Suspension on body (including the scalp in 36 out of 43 subjects) adrenal suppression was identified in 3 out of 43 subjects (7%) after 4 weeks of treatment and in none of the 36 subjects who continued treatment for 8 weeks. In a trial evaluating the effects of Taclonex® Topical Suspension on the HPA axis, 31 subjects aged 12 to 17 years were treated with Taclonex® Topical Suspension on the scalp. Adrenal suppression was identified in 1 of 30 evaluable subjects (3.3%) after 4 weeks of treatment. If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. Cushing's syndrome and hyperglycemia may also occur due to the systemic effects of the topical corticosteroid. These complications are rare and generally occur after prolonged exposure to excessively large doses, especially of high-potency topical corticosteroids. Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure. **Allergic Contact Dermatitis with Topical Corticosteroids:** Allergic contact dermatitis to a topical corticosteroid is usually diagnosed by observing a failure to heal rather than a clinical exacerbation. Such an observation should be corroborated with appropriate diagnostic patch testing. **Allergic Contact Dermatitis with Topical Calcipotriene:** Allergic contact dermatitis has been observed with use of topical calcipotriene. Such an observation should be corroborated with appropriate diagnostic patch testing. **Eye Irritation:** Avoid eye exposures. Taclonex® Topical Suspension may cause eye irritation. **Risks of Ultraviolet Light Exposures:** Patients who apply Taclonex® Topical Suspension to exposed skin should avoid excessive exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc. Physicians may wish to limit or avoid use of phototherapy in patients who use Taclonex® Topical Suspension.

CONTRAINDICATIONS: None.

ADVERSE REACTIONS: Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directed compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. *Clinical Trials Conducted in Subjects 18 years and older with Scalp Psoriasis:* The rates of adverse reactions given below were derived from randomized, multicenter, prospective vehicle- and/or active controlled clinical trials in adult subjects with scalp psoriasis. Subjects applied study product once daily for 8 weeks, and the median weekly dose was 12.6 g.
Adverse reactions that occurred in ≥1% of subjects treated with Taclonex® Topical Suspension and at a rate higher than in subjects treated with vehicle are presented in Table 1:

Table 1

Number and Percentage with Adverse Reactions in Scalp Psoriasis Trials (Events Reported by ≥1% of Subjects and for Which a Relationship is Possible)				
	Taclonex® Topical Suspension **N=1,953**	**Betamethasone dipropionate in vehicle N=1,214**	**Calcipotriene in vehicle N=979**	**Vehicle N=173**
Event	# of subjects (%)			
Folliculitis	16 (1%)	12 (1%)	**5 (1%)**	0 (0%)
Burning sensation of skin	13 (1%)	10 (1%)	29 (3%)	0 (0%)

Other less common adverse reactions (<1% but >0.1%) were, in decreasing order of incidence: acne, exacerbation of psoriasis, eye irritation, and pustular rash. In a 52-week trial, adverse reactions that were reported by >1% of subjects treated with Taclonex® Topical Suspension were pruritus (3.6%), psoriasis (2.4%), erythema (2.1%), skin irritation (1.4%), and folliculitis (1.2%). *Clinical Trials Conducted in Subjects 18 years and older with Psoriasis on the Body:* In randomized, multicenter, prospective vehicle- and/or active controlled clinical trials in adult subjects with plaque psoriasis on non-scalp areas, subjects applied study product once daily for 8 weeks. A total of 824 subjects were treated with Taclonex® Topical Suspension and the median weekly dose was 22.6 g.
There were no adverse reactions that occurred in ≥1% of subjects treated with Taclonex® Topical Suspension and at a rate higher than in subjects treated with vehicle. Other less common adverse reactions (<1% but >0.1%) were, in decreasing order of incidence: rash and folliculitis. *Clinical Trials Conducted in Subjects 12 to 17 years with Scalp Psoriasis:* In two uncontrolled prospective clinical trials, a total of 109 subjects aged 12-17 years with plaque psoriasis of the scalp were treated with Taclonex® Topical Suspension once daily for up to 8 weeks. The median weekly dose was 40 g. Adverse reactions included acne, acneiform dermatitis and application site pruritus (0.9% each).

USE IN SPECIFIC POPULATIONS: Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Animal reproduction studies have not been conducted with Taclonex® Topical Suspension. Taclonex® Topical Suspension contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically. There are no adequate and well-controlled studies in pregnant women. Taclonex® Topical Suspension should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. **Nursing Mothers:** Systemically administered corticosteroids appear in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topically administered calcipotriene or corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Taclonex® Topical Suspension is administered to a nursing woman. The patient should be instructed not to use Taclonex® Topical Suspension on the breast when nursing. **Pediatric use:** Safety and effectiveness of the use of Taclonex® Topical Suspension in pediatric patients under the age of 12 years have not been established. The safety and effectiveness of Taclonex® Topical Suspension for the treatment of plaque psoriasis of the scalp have been established in the age group 12 to 17 years. Two prospective, uncontrolled trials (N=109) were conducted in pediatric subjects age 12 to 17 years with scalp psoriasis, including assessment of HPA axis suppression in 30 subjects. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity when treated with topical drugs. They are, therefore, also at greater risk of HPA axis suppression and adrenal insufficiency upon the use of topical corticosteroids. Rare systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids. Local adverse reactions including striae have also been reported with use of topical corticosteroids in pediatric patients. **Geriatric use:** Clinical studies of Taclonex® Topical Suspension in plaque psoriasis on non-scalp areas included 124 subjects who were 65 years of age or over, and 36 were 75 years of age or over. Clinical studies of Taclonex® Topical Suspension in scalp psoriasis included 334 subjects who were 65 years or over and 84 subjects who were 75 years or over. No overall differences in safety or effectiveness of Taclonex® Topical Suspension were observed between these subjects and younger subjects, and other reported clinical experience has not identified any differences in response between elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

DOSAGE AND ADMINISTRATION: Instruct patients to shake bottle prior to using Taclonex® Topical Suspension and to wash their hands after applying the product. Apply Taclonex® Topical Suspension to affected areas once daily for up to 8 weeks. Therapy should be discontinued when control is achieved. Patients 18 years and older should not use more than 100 g per week and patients 12 to 17 years should not use more than 60 g per week. Taclonex® Topical Suspension should not be used with occlusive dressings unless directed by a physician. Taclonex® Topical Suspension is not for oral, ophthalmic, or intravaginal use. Avoid use on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

NONCLINICAL TOXICOLOGY: Calcipotriene may enhance the effect of UVR to induce skin tumors. Long-term animal studies have not been performed to evaluate the carcinogenic potential of betamethasone dipropionate.

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling (Patient Information and Instructions for Use)
Inform patients of the following:

- Instruct adult patients (18 years and older) not to use more than 100 g per week.
- Instruct pediatric patients (12 to 17 years) not to use more than 60 g per week.
- Discontinue therapy when control is achieved unless directed otherwise by the physician.
- Do not apply Taclonex® Topical Suspension to the scalp in the 12 hours before or after any chemical treatments to the hair. Since hair treatments may involve strong chemicals, talk with physician first.
- If applied to the scalp, do not wash hair or take a bath or shower right after application.
- Avoid use of Taclonex® Topical Suspension on the face, underarms, groin or eyes. If this medicine gets on face or in eyes, wash area right away.
- Do not occlude the treatment area with a bandage or other covering unless directed by the physician.
- Note that local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids.
- Wash hands after application.
- Instruct patients not to use other products containing calcipotriene or a corticosteroid with Taclonex® Topical Suspension without first talking to the physician.
- Instruct patients who use Taclonex® Topical Suspension to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc.).

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EDITORIAL: PART II OF II

Dressing Minor Wounds: Avant Garde or Tried and Trusted?

Peter Lowthian*, MPhil, SRN;[1] Lawrence Charles Parish, MD, MD (Hon)[2]

How important are dressings for minor wounds? We have recently addressed this issue, but now we would like to focus on the dressings themselves. This seems timely considering the plethora of proprietary wound dressings currently available and the claims made for them. Fortunately or unfortunately, these dressings are mostly designed for serious wounds, including ulcers and lacerations; nevertheless, some marketers have not neglected the idea of using sophisticated dressings for minor wounds.

DRESSING HISTORY

Following invention of the band-aid in 1920, manufacturers began to produce variations on the original. One of these, marketed in the mid-20th century, was made from a microporous plasticized polyvinyl chloride. This material proved to be rather weak and often tore. Even so, these dressings prevented skin maceration and appeared to improve wound healing.

Then, in 1959, 3M introduced Micropore®. This thin tape, still very much in use, has been joined by many comparable products using similar acrylic-based adhesives. The pores in Micropore® (about 20 μm in diameter) are easy to see with a magnifying glass. These do permit the entry of bacteria but, fortunately, Micropore® is not conducive to bacterial growth. Bacteria-free it may not be, but this tape can still be sterilized.

Surprisingly, Micropore® is hydrophobic, and gravity does not pull tiny drops of water through its pores. This may be confirmed by placing a droplet of water on a dry piece (Figure 1). Water and serum *can* slowly pass through Micropore®, especially if it is either forced through under gentle pressure or directed through by absorbent material. Not surprisingly, water vapor passes through easily. Micropore®, therefore, prevents maceration and is water-resistant, rather than waterproof.

In the 1970s, a new (waterproof) adhesive polyurethane film, Opsite®, was introduced. This product, which can be considered as "semi-occlusive" also prevents skin maceration, and its pores are small enough to exclude bacteria while being reasonably permeable to water vapor.

Opsite®, or a similar semi-occlusive film, can be used on non-bleeding small wounds, although it can be problematic to apply small pieces. Removing film dressings can also be challenging: it sometimes results in skin tears. Additionally, Opsite® can create an artificial bulla by allowing wound fluid to accumulate beneath it. This is often unsightly. Even though Opsite® should be

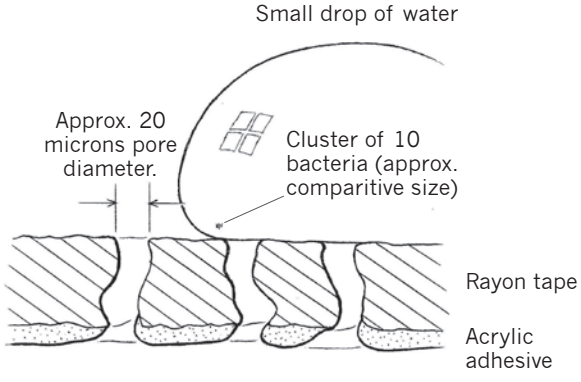

Figure 1. Much enlarged section of Micropore® tape (Artist's view).

From the Royal National Orthopaedic Hospital, Stanmore, United Kingdom (formerly);[1] and the Department of Dermatology and Cutaneous Biology and the Jefferson Center for International Dermatology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA[2]

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See also Part I: *SKINmed* 2013;11:325–326

*Deceased.

changed after 7 days, an artificial bulla attracts attention, encouraging early, and unnecessary exploration.[1]

An absorbent pad is often needed in a dressing, as was recognized in the distant past, and during the War between the States (1861–1865) lint was used fluffy side down. Apart from absorbing fluid, this enabled pressure to be evenly applied to wounds, despite their complexity.

Some surgeons worried that lint might become enmeshed in the wound, but others noted that this only happened with necrotic tissue, which should not cause concern. Possibly, enmeshing was only problematical in wounds with undermining. This may partly explain why clinicians came to favor nonadherent, absorbent pads.[2] Many such dressings have been made, including those impregnated with Vaseline or other medicaments.

WHICH DRESSING?

Pre-prepared dressings may be labor-saving, but this supposed benefit may be negated, when various sizes and shapes have to be available. Two-part dressings can thus be more convenient and less expensive than pre-prepared ones, providing that the two-part dressing is easy to prepare. Accordingly, for minor wounds, it seems sensible to examine adhesive tapes and absorbent pads separately; however, this does mean we are not considering plastic skins, as well as skin adhesives.[3]

Lint, being readily available in the United Kingdom, is seen as a suitable absorbent pad for most minor wounds, even without antiseptic additions. Should bacterial contamination be a consideration, suitable antimicrobial ointments may be thinly applied.

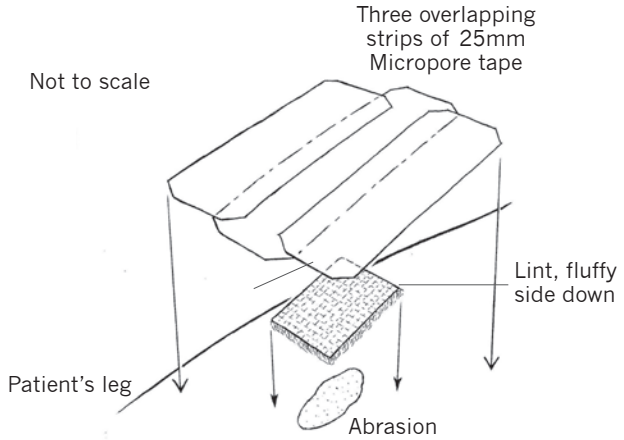

Figure 2. "Exploded" view of typical Micropore®/lint dressing for an abrasion.

Among adhesive tapes, stretchable ones are attractive but easily misused, particularly if they are stretched before application. The adhesive (if strong) then pulls on the epidermis and can slowly tear it off the dermis, resulting in a traction bulla. A nonstretch tape, such as Micropore® is preferable, considering also that it is translucent rather than transparent, so deterring unnecessary wound exploration.

Micropore® can be torn by hand, but cutting it and trimming its corners is neater (Figure 2) and helps to avoid clothing snags. Strips of Micropore® can be cut for covering tricky areas, such as finger joints; the overlapping strips being arranged transversely across the (semi-flexed) joint, so as to allow some joint movement. In addition, Micropore® adheres to damp (not wet) skin, and its adherence is enhanced by moderate pressure, yet it is easy to remove without damaging tender skin.

In addition, the value for money advantage appears to lie with the Micropore®/lint dressing.

If a dressing is being used for camouflaging minor wounds (eg, razor nicks), Micropore® is suitable and is not obtrusive. We may add that, for very small wounds, this tape can (in theory) be used without an absorbent pad.

Another property of a good tape is that it should be unlikely to cause allergies. Our experience indicates that this applies to genuine Micropore® tape.

Primarily, we have found that Micropore® tape encourages the epithelialization of superficial wounds, if the tape completely covers the wound (Figure 2). This appears to allow just the right amount of moisture to evaporate through the tape pores, to prevent maceration, and to maintain a moist wound.[4,5]

SEMI-OCCLUSIVE OR WATER-RESISTANT?

Why not use a semi-occlusive dressing so as to prevent any bacteria from getting through the dressing (eg, Opsite®)?

In reality, one cannot really prevent some bacteria living on the wound when the dressing is applied, and who can rely on any dressing maintaining an unbroken seal? Edges often lift off, or are forced off when, for instance, fluid collects under a semi-occlusive film.

If, however, a semi-occlusive dressing is not disrupted, the wound and its surrounding skin will be moist and warm. This results in an increased number of viable white blood cells (WBCs) under the dressing,[6] so that only a few bacteria are likely to survive there. Dry dressings probably kill bacteria by dehydration. Even

so, wounds that are allowed to dry out take longer to heal. Also, as wound exudate dries, it can enmesh gauze and similar materials. Removing such dressings then causes further wound trauma, interfering with reepithelialization.[1,5] This is why so many prepared dressings are now semi-occlusive.

Some, such as Allevyn® and Mepilex® (well-known in the United Kingdom) use an absorbent layer to take up exudate/hemorrhage and cover this with a semi-occlusive film. This preserves a moist wound environment and prevents bacterial or blood contamination (via the dressing). As a result, these dressings could well replace traditional waterproof tapes. They still, however, need regular dressing changes.

Of course, the Micropore®/lint dressing also maintains a moist wound surface and, following a few days under this dressing, the wound fluid has a jelly-like consistency, with no sign of lint sticking to the wound. If this gelled serum contains more WBCs than are found under semi-occlusive dressings, wound infection rates may be correspondingly lower. It would be interesting to test this supposition in further studies, but actual results using Micropore®/lint dressings suggest that they could be very close to optimizing conditions for the body's natural repair and defence tissues.[7]

A few years ago, as an experiment, one of us (PTL) left a Micropore®/lint dressing on his leg abrasion for 3 weeks: a so-called "No-change" dressing. The lint was fluffy side down. This dressing did, at times, get soaked in shower water, but dried out without being disturbed.

After 3 weeks, the dressing was easily peeled away. The abrasion, which had been about 1.5 × 0.5 inch had completely healed. Nothing appeared to be enmeshed in the wound area, save for a few strands of lint. These were stuck in the new skin, but they soon came away, with warm soapy water. Later, we realized that these strands were probably caught in the upper part of the healed epidermis.

This outcome suggests that lint pads could also be used under semi-occlusive film dressings, but we have no experience with this.

CONCLUSIONS

"No-change" minor wound dressings that need little or no changing are obviously more convenient and economical. They also promote wound healing by avoiding traditional daily dressing changes, which may delay the healing process through cooling and dehydration. Although sophisticated semi-occlusive dressings can be used for some minor wounds, mostly to guard against external contamination, or to avoid contaminating other things, a No-change Micropore®/lint dressing should be considered for most other minor wounds. With hindsight, we might just owe more to the Union and Confederate surgeons than previously thought.

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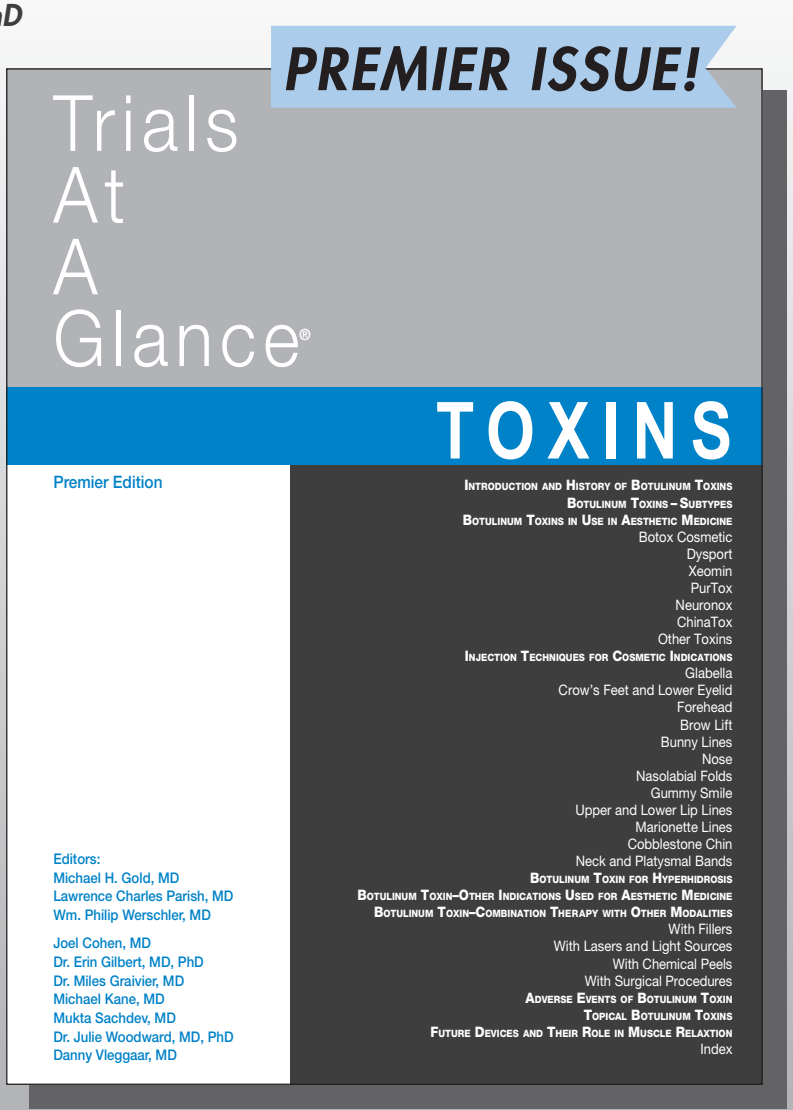

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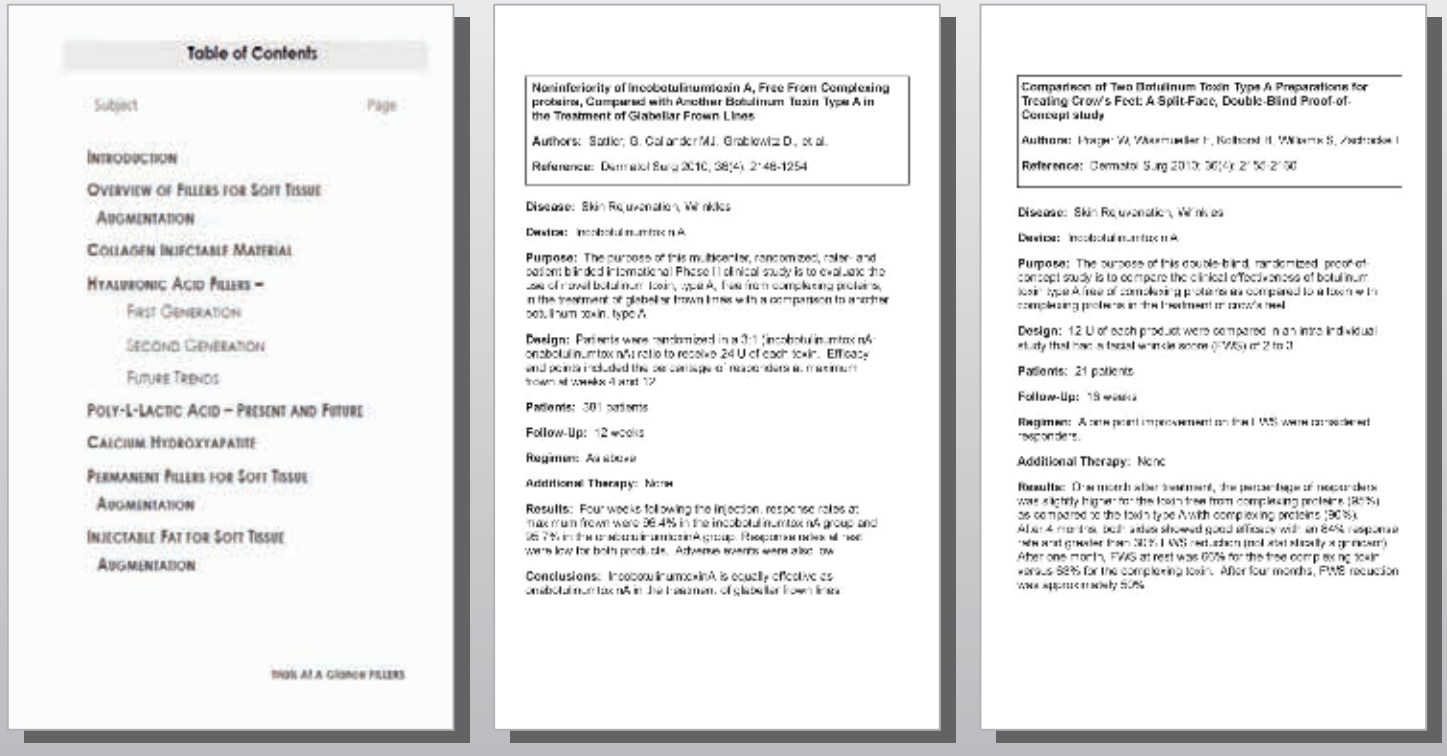

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The Value of Historical Vignettes

Robert J. Thomsen, MD

Don't gloss over the paper "The History of Tuberous Sclerosis Complex: When Skin Gives a Clue"[1] in this issue of the Journal because it is a "Historical Vignette" and assume that it is, as the common phrase goes, "of historical interest only." The word reminiscence may bring instantly to mind sitting before the fire on a quiet evening listening to grandfather or grandmother tell stories of the olden days, stories that may seem to have no relationship to the modern world (whatever that may be). To take the time to read a paper like this may seem to be a luxury, an extra, or even an irrelevance that can be dismissed or marginalized. We do this at our peril. In the modern times of an increasing barrage of information it is absolutely true that we must set our filter so that we obtain important information and let the rest go. But so often we are dragged down by the immediate needs—drinking from the fire hose—and are too fatigued to consider other information. To keep ourselves fresh and interested in our professional lives we must want to consider historical information.

SHARPEN THE SAW

Stephen Covey presented as one of his key habits in Seven Habits of Highly Effective People the need to "Sharpen the Saw."[2] He presented the image of the lumber jack who is working very hard because he has a dull saw, but does not feel there is time to stop to sharpen the saw. And so he works harder and harder and is less and less effective. If he just stops to sharpen the saw, the work will eventually become easier and more productive. It is an important lesson in all phases of our lives. Historical papers such as this help us to sharpen that saw and make our practices more interesting to us.

There are several general lessons from this paper that can be found in any good paper. First, it presents information about the shift in definition of a problem and how it may change with time. Our concepts are especially influenced by the development of new technology. The heart as a pump could not be conceived until the development of pumps. We see how, in the example of tuberous sclerosis, the ideas shift because of shifts in technical capabilities. During the 19th century, clinicians relied on observations with their 5 senses—what they could see, hear, smell, touch, and maybe even taste. With the development of microscopy, diagnostic refinement became greater as tissue, which appeared grossly to be similar, were obviously not. The next revolution came with capabilities in imaging, with computerized tomography (CT) and magnetic resonance imaging (MRI) the body could be probed noninvasively in ways undreamed of when the first fuzzy x-ray images were created. The latest technological advance is that of genomic testing. With the recent advent of relatively inexpensive testing of the entire human genome will come unprecedented advances in our understanding. This is dramatically illustrated in this paper.

This paper also presents the importance of regarding the human body as a whole. In the busy rush of every day practice it is tempting to regard the person before us as skin that cloaks an unknown, and it is our job to concentrate on the skin. We may be successful at satisfying the needs of that person by so concentrating, but more frequently than we suspect, the person needs to be viewed as a complex—body, mind, and spirit; individual or member of family, clan, class, group, and consumer. When persons were viewed as having more than sebaceous adenomas, or cranial tubers, or epilepsy, they could be considered and cared for from a broader perspective.

Another important lesson in this paper relevant to today has to do with information sharing. Early on, information was shared through textbooks, journals, meetings, and personal visits. These remain vital today, but the technology of information sharing has logarithmically increased the information available, and it will only be getting greater as information explodes. Computer management of large datasets is in its infancy. It is vital that we learn the lessons of how to share information and how to obtain the relevant information that will help us and advance the frontiers of knowledge.

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CONCLUSIONS

Finally, this paper has great importance to the specific topic of tuberous sclerosis. Once regarded as an extreme rarity because of its rigid definitions, tuberous sclerosis may be regarded as potentially much more common in its milder forms. Identifying those milder forms has important implications to the individual for diagnosis and management, as well as to the person's family in terms of genetic counseling and to society as a whole. We as dermatologists have the potential to contribute to their overall wellness, and not only the wellness of their skin.

Reminiscing by reading a paper like this helps to stay fresh, heighten our awareness, question our assumptions, use new technology, and ultimately be of help to those who need our expertise. It is essential to keep us moving forward instead of floundering in the anxieties of the present. Enjoy this paper.

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1 Bartolini E, Giannelli C. The history of tuberous sclerosis complex: when skin gives a clue. *SKINmed*. 2015;1:67–72.

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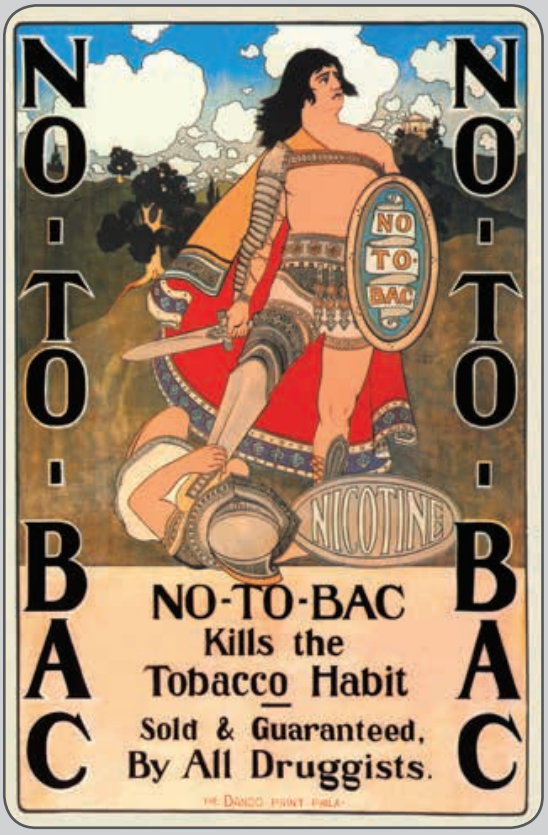

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ORIGINAL CONTRIBUTION

Rosemary Oil vs Minoxidil 2% for the Treatment of Androgenetic Alopecia: A Randomized Comparative Trial

Yunes Panahi, PhD;[1] Mohsen Taghizadeh, PhD;[2] Eisa Tahmasbpour Marzony, MSc;[1] Amirhossein Sahebkar, PharmD, PhD[3]

ABSTRACT

Rosmarinus officinalis L. is a medicinal plant with diverse activities including enhancement microcapillary perfusion. The present study aimed to investigate the clinical efficacy of rosemary oil in the treatment of androgenetic alopecia (AGA) and compare its effects with minoxidil 2%. Patients with AGA were randomly assigned to rosemary oil (n=50) or minoxidil 2% (n=50) for a period of 6 months. After a baseline visit, patients returned to the clinic for efficacy and safety evaluations every 3 months. A standardized professional microphotographic assessment of each volunteer was taken at the initial interview and after 3 and 6 months of the trial. No significant change was observed in the mean hair count at the 3-month endpoint, neither in the rosemary nor in the minoxidil group (P>.05). In contrast, both groups experienced a significant increase in hair count at the 6-month endpoint compared with the baseline and 3-month endpoint (P<.05). No significant difference was found between the study groups regarding hair count either at month 3 or month 6 (P>.05). The frequencies of dry hair, greasy hair, and dandruff were not found to be significantly different from baseline at either month 3 or month 6 trial in the groups (P>.05). The frequency of scalp itching at the 3- and 6-month trial points was significantly higher compared with baseline in both groups (P<.05). Scalp itching, however, was more frequent in the minoxidil group at both assessed endpoints (P<.05). The findings of the present trial provided evidence with respect to the efficacy of rosemary oil in the treatment of AGA. (*SKINmed.* 2015;13:15–21)

Androgenetic alopecia (AGA) is the most common type of hair loss in both men and women, affecting about 50% of patients before the age of 50.[1] This type of hair loss is more prevalent in men, however, and has significant social and psychological consequences.[1,2] AGA mostly occurs in the temple and crown areas of the head, representing an M-shaped pattern. The most widely used medications for AGA are topical minoxidil and 5α-reductase inhibitors; however, these drugs are associated with several adverse effects such as itching, circulatory problems, hirsuitism, decreased libido, male fetal anolamies, and recurrence of hair loss after stopping drug use.[1–3] Aside from these side effects, therapeutic efficacy of the current medications is not comprehensive. Therefore, avenues for research are open for finding novel agents with better efficacy and fewer side effects.

Rosmarinus officinalis L. (rosemary) is an aromatic evergreen and perennial herb belonging to the family labiateae. Rosemary is native to the Mediterranean region but is also extensively cultivated elsewhere. It is a well-known medicinal plant with a wide history of application in several traditional systems of medicine. This plant has been used as an anti-flatulent, anti-asthma, diaphoretic, emmenagogue, memory-enhancing, sedative, analgesic, anti-rheumatic, and digestive agent.[4–7] Furthermore, modern scientific research has unveiled several interesting pharmacologic activities for rosemary, such as antioxidant,[8] cholagogue, hepatoprotective,[9] neuroprotective,[10] antibacterial, antiviral, antifungal,[11,12] and smooth muscle cell relaxant[13,14] properties.

Rosemary oil is often used in the cosmeceutical industry because of its pleasant aroma and beneficial effects against eczema, acne,

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dermatitis, skin puffiness, and swelling. Since the spasmolytic activity of rosemary may enhance microcapillary perfusion,[15] this plant has been hypothesized to increase hair follicle blood supply, thereby being effective for the treatment of AGA. Therefore, the present study set out to investigate the clinical efficacy of rosemary oil in the treatment of AGA and compare its effects with minoxidil 2% as the most widely used medication.

PATIENTS AND METHODS

This was a 6-month randomized single-blind clinical trial in men referred to the dermatology clinic of the Baqiyatallah Hospital (Tehran, Iran) between April 2010 and June 2011. After obtaining institutional review board approval and informed consent, 100 patients were recruited. Recruited patients were aged 18 to 49 years with naturally dark hair and AGA characterized as vertex pattern grades II through IV according to the Hamilton Rating Scale for Depression.[16] Exclusion criteria were concomitant use of hair restorers, use of systemic drugs such as 5α-reductase inhibitors during the preceding 6 months, and hypersensitivity to minoxidil. After an initial screening evaluation, physical examination, and laboratory evaluation, eligible men were randomly assigned to rosemary oil (n=50) or minoxidil 2% (n=50). Rosemary oil lotion was standardized as having at least 3.7 mg 1,8-cineole per mL of the product, and provided by the Barij Essence Pharmaceutical Company, Kashan, Iran. All patients signed a written consent form before starting the trial.

Patients applied 1 mL of either assigned solutions twice daily at approximately 12-hour intervals (total daily dose of 2 mL) to the frontoparietal and vertex areas of the scalp (with gentle massage) for a period of 6 months. After baseline visit, patients returned to the clinic for efficacy and safety evaluations every 3 months. Rosemary and minoxidil lotions were matched regarding shape and color. A standardized professional microphotographic assessment of each volunteer was taken at the initial interview and after 3 and 6 months of the trial. Changes in these photographic assessments formed the primary outcome measure, with improvement as the most important factor. These changes were scored independently by two dermatologists who were unaware of the therapy administered. The efficacy of either intervention was also assessed by asking the participants' satisfaction from hair loss decrease and hair growth improvement. For each efficacy measure, participants were asked to express their satisfaction from treatment by giving a score of –3 (severe aggravation), –2 (moderate aggravation), –1 (mild aggravation), 0 (no change), +1 (mild improvement), +2 (moderate improvement), or +3 (severe improvement).

All data were analyzed using Student t test (within-group comparisons of hair count), analysis of variance with Bonferroni's adjustment for multiple comparisons (between-group comparisons of hair count), or chi-square test (frequency of adverse events). A probability <.05 was considered significant. Data were analyzed using SPSS software, version 16 (SPSS Inc, IBM Corporation, Armonk, NY).

RESULTS

Recruited patients were 100 men with a mean age of 24.03±3.21 years. A total of 71% of patients had stage II and 21% had stage III AGA based on the Hamilton scale. A total of 35% of participants previously used hair loss medications. The frequency for dandruff, scalp itching, dry hair, and greasy hair in the total study population were 16%, 31%, 16%, and 72%, respectively. There was no significant difference between the rosemary and minoxidil groups in terms of age, duration of hair loss, stage of AGA, and the frequency of dandruff, scalp itching, dry hair, and greasy hair at baseline (*P*>.05; Table I).

Table I. Demographic Characteristics of Study Patients

Parameters	2% Minoxidil	Rosemary	*P* Value
No.	50	50	–
Mean age, y	23.38±2.5	24.78±3.67	.76
Duration of hair loss, y	3.88±2.21	4.41±2.59	.27
Baseline hair count	138.4±38.03	122.8±48.9	.18
Stage of baldness			
II	34	37	.66
III	16	13	
IV	0	0	

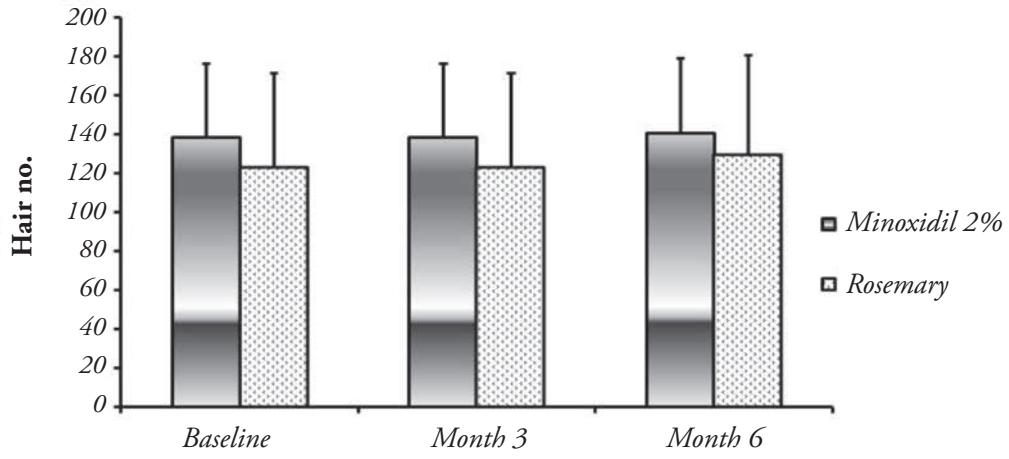

Figure 1. Comparison of hair count between the study groups at different intervals. Significant increases in mean hair count were observed at month 6 compared with month 3 and baseline in both groups (P<.05).

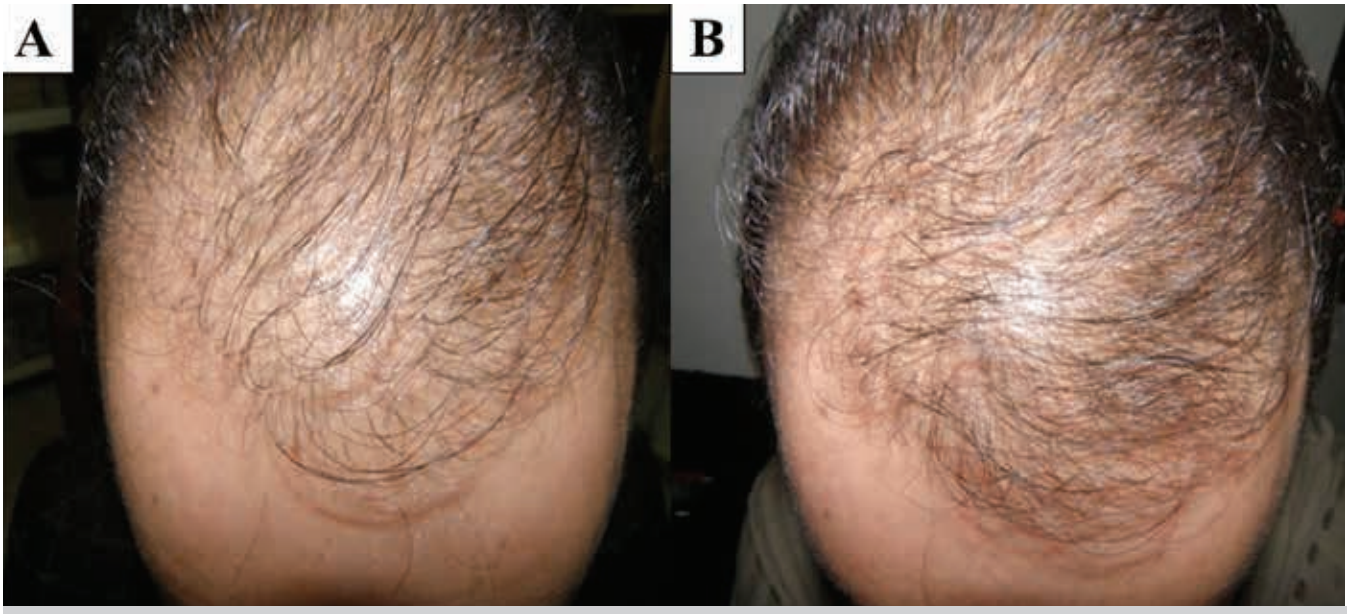

Figure 2. A sample pre-trial and post-trial scalp photograph in the rosemary group.

The groups were comparable regarding their baseline hair count (122.8±48.9 in the rosemary and 138.4±38.0 in the minoxidil group; P>.05). No significant change was observed in the mean hair count at the month 3 endpoint, neither in the rosemary (122.8±48.9) nor in the minoxidil (138.4±38.0) group (P>.05). In contrast, both groups experienced a significant increase in hair count at the month 6 endpoint compared with the baseline and month 3 endpoint (129.6±51.2 in the rosemary and 140.7±38.5 in the minoxidil group; P<.05). No significant difference was found between the study groups regarding their hair counts either at month 3 or month 6 (P>.05; Figure 1). Some sample pre-trial and post-trial scalp photographs of patients are shown in Figures 2 and 3.

No significant difference in the frequencies of dry hair, greasy hair, and dandruff was found at either month 3 or month 6 compared with baseline in both rosemary and minoxidil groups (P>.05; Figure 4). The frequency of scalp itching at month 3 and month 6 was significantly higher compared with baseline in both groups (P<.05; Figure 5); however, there was no significant difference between month 3 and month 6 (P>.05; Figure 6). Scalp itching was more frequent in the minoxidil group at both assessed endpoints (P<.05; Figure 7).

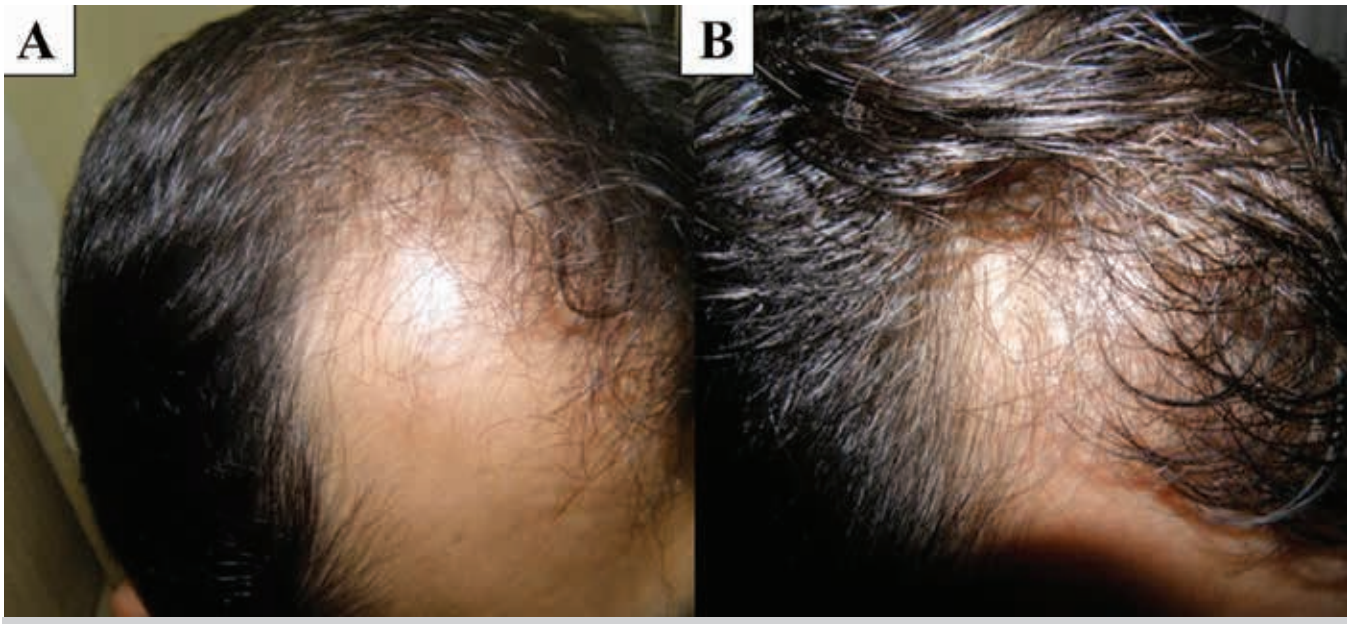

Figure 3. A sample pre-trial and post-trial scalp photograph in the minoxidil group.

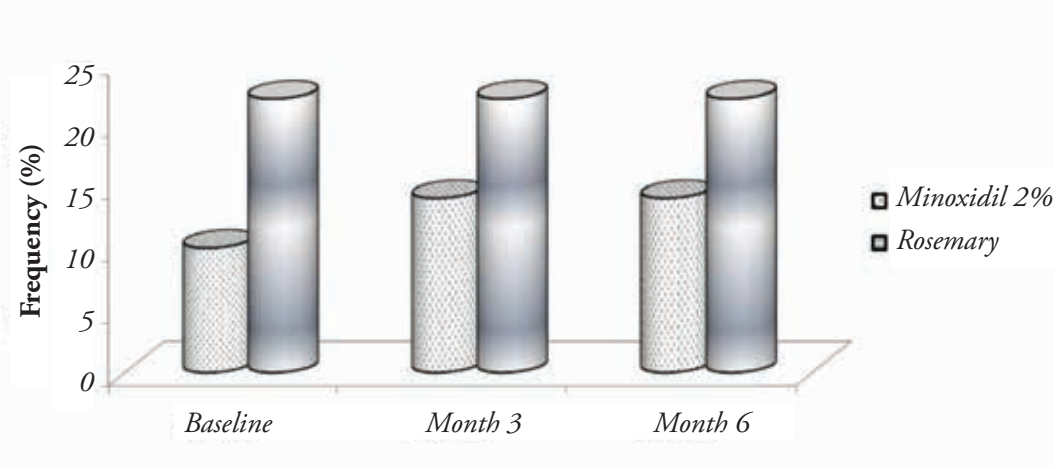

Figure 4. Frequency of dry hair in the study groups at baseline and months 3 and 6. No significant within-group or between-group difference was observed ($P>.05$).

In addition to hair count and hair disorders, questions in the patients' questionnaire were categorized to evaluate two aspects of hair growth: increase in hair growth and decrease in hair loss (mild, moderate, no change, and worse). The percentage of satisfaction with treatment (calculated from patient perspectives during treatment) demonstrated a marginally significant difference favoring the rosemary group over the 2% topical minoxidil group. Hair loss in both groups during the study was decreased. The proportion score for rosemary was significantly superior to 2% topical minoxidil group at months 3 and 6 with regard to decrease in hair loss ($P<.05$). Hair growth was equally increased in both groups during the study according to the patients' answers ($P>.05$; Table II).

DISCUSSION

Alternative medicine and botanical preparations have long been used in different traditional systems of medicine for the treatment of dermatologic disorders including alopecia. Recently, there has been a surge of interest in the use of alternative approaches, at least as adjuncts, for the treatment of hair loss. The present study aimed to evaluate the efficacy and safety of rosemary oil in the treatment of AGA and compare its effects with the widely prescribed drug minoxidil.

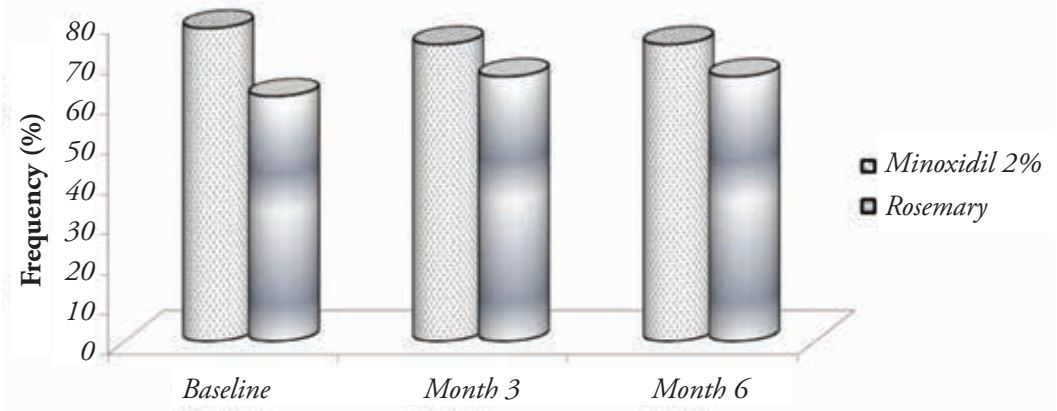

Figure 5. Frequency of greasy hair in the study groups at baseline and months 3 and 6. No significant within-group or between-group difference was observed (*P*>.05).

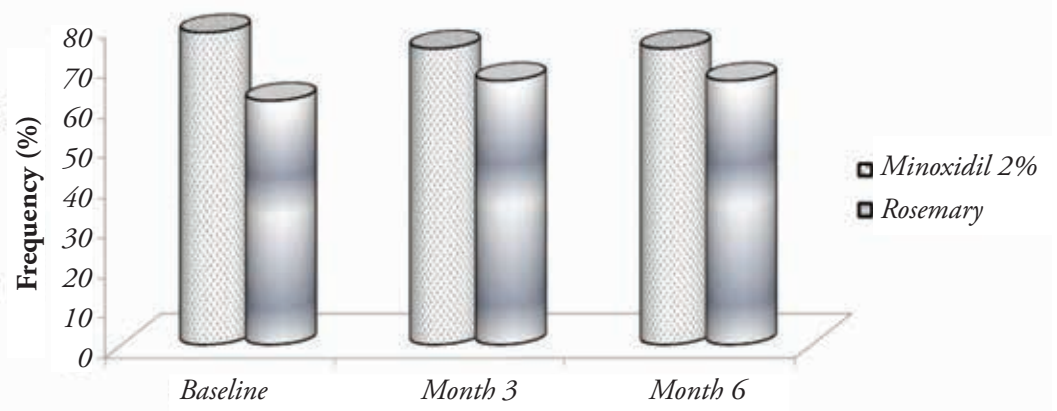

Figure 6. Frequency of dandruff in the study groups at baseline, 3 months and 6 months intervals. No significant within- or between-group difference was observed (*P*>.05).

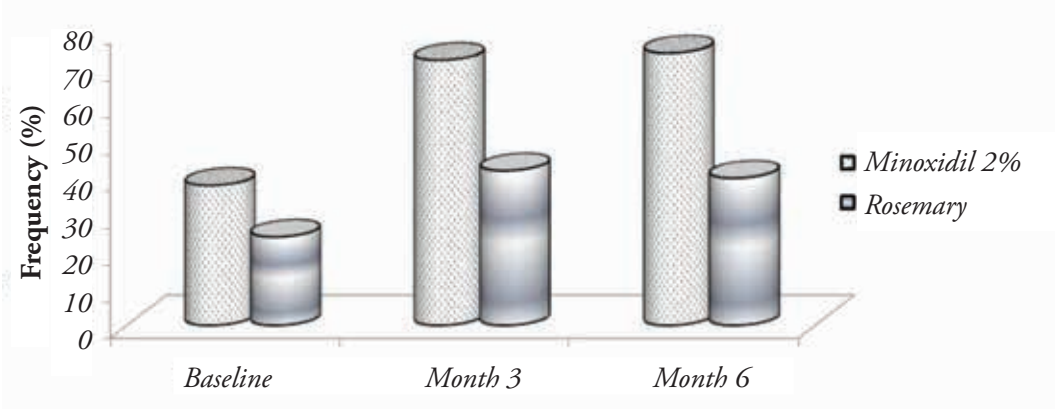

Figure 7. Frequency of scalp itching in the study groups at baseline, 3 months and 6 months intervals. Significantly higher frequencies were observed at months 3 and 6 compared to baseline, and in the rosemary compared to minoxidil 2% group at both assessed time points (*P*<0.05).

Table II. Percentage of Men With Improvement (Satisfying) in Scalp Hair During the Study According to Answers to a Self-Assessment Questionnaire

Parameters	2% Minoxidil				Rosemary			
	Mild	Moderate	No Change	Worse	Mild	Moderate	No Change	Worse
Increase in hair growth								
Month 3	1 (2%)	0%	47 (94%)	2 (4%)	3 (6%)	0%	47 (94%)	0%
Month 6	12 (24%)	0%	38 (76%)	0%	19 (38%)	0%	31 (62%)	0%
Decrease in hair loss								
Month 3	43 (86%)	0 (0%)	5 (10%)	2 (4%)	18 (36%)[a]	32 (64%)[a]	0 (0%)	0 (0%)
Month 6	46 (92%)	4 (8%)	0%	0%	9 (18%)[a]	41 (82%)[a]	0 (0%)	0 (0%)

[a]Significant difference ($P<.05$).

Leaves and branchlets of rosemary contain considerable amounts of essential oil. The essential oil content of rosemary has been reported to be 0.5% to 2.5% v/w and 1% based on the British Pharmacopea. The same as other oils, chemical composition and relative frequencies of volatile components in the rosemary oil varies with geographical and climatic changes, soil composition, extraction method, and source part of the plant[17,18]; however, the major volatile components of rosemary oil have been reported to be 1, 8-cineole, borneol, bornyl acetate, camphor, α-pinene, and β-pinene.

To our knowledge, no study has yet specifically investigated the efficacy of rosemary oil in the treatment of AGA. There has been just a single trial in this field,[19] in which the authors reported the efficacy and safety of 7-month application of an aromatherapy cocktail containing thyme, rosemary, lavender, and cedarwood oils in a mixture of carrier oils jojoba and grapeseed in the treatment of alopecia areata.[19] In the present study, application of topical rosemary solution was as effective as minoxidil 2% in the treatment of AGA. In addition, there was better treatment compliance in the rosemary group compared with the minoxidil group. This may be the result of decreased frequency of scalp itching and higher patient satisfaction with decreased hair loss in the rosemary group.

There is evidence favoring the efficacy of other herbal products in the treatment of hair loss. For instance, raspberry ketone—a natural aromatic phenol isolated from Rubus idaeus—was reported to promote hair re-growth. The mechanism of action of raspberry ketone appears to be the upregulation of IGF-I expression in the dermal papillae of hair follicles.[20] The impact of Dabao (a hair tonic mixture in Chinese medicine containing saffron flower, Mullberry leaves, stemona root, pepper fruits, sesame leaves, schan pepper skin, ginger root hawthorn fruit, and Chinese angelica root) has also been reported to be beneficial on overall growth of non-vellus hair.[21] Another herbal remedy that has shown efficacy in the treatment of AGA is the bioactive polyphenol procyanidin B-2 that has been shown to increase total and terminal hair counts through promotion of hair epithelial cell growth, shifting the hair cycle from telogen to anagen phase and antioxidant activity.[22] There are also findings on the efficacy of other types of other natural products such as Aloe vera, garlic, primula, onion, green tea, broomcorn millet, and capsaicin in the treatment of different types of alopecia.[23]

Rosemary possesses spasmolytic activity on smooth muscles.[15] Such an effect could lead to the relaxation of scalp vessels and enhanced perfusion of hair follicles. One of the phytochemicals that may account for these effects is camphor, which is known to exert local hyperemic effects. Another mechanism for the beneficial effects of rosemary oil is its antioxidant activity. Oxidative stress has been suggested to be associated with alopecia as significantly lower levels of antioxidants and elevated oxidants have been found in patients with alopecia.[24] Rosemary oil is well documented with respect to the antioxidant activity and has been shown to exert both free radical scavenging and lipid peroxidation inhibitory activities.[25] rosemary oil has several other pleiotropic effects, in addition to its potentiating effects on the scalp microcapillary circulation. For instance, antibacterial and antifungal properties of rosemary oil are well-established. In addition, this oil has nourishing and conditioning properties, leading to the softening and silky appearance of hair strands.[19]

CONCLUSIONS

The findings of the present trial provide evidence with respect to the efficacy of rosemary oil in the treatment of AGA. Further research is warranted to identify the active ingredients and their mechanism of action.

ACKNOWLEDGMENTS

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ORIGINAL CONTRIBUTION

Efficacy Evaluation of a Cosmetic Slimming Treatment for the Waist and Hips: A Double-Blind Study

Adele Sparavigna, MD;[1] Regina Vesnaver, PhD;[2] Anna Cenni;[3] Marco Oliva[3]

ABSTRACT

The aim of this study was to evaluate by clinical and noninvasive instrumental evaluations the efficacy and tolerance of a cosmetic topical slimming treatment specific for light/moderate adipose pannicula at the level of the waist and hips. The protocol was performed as a double-blind active vs placebo trial in 110 volunteers for a period of 4 weeks, with an additional visit 4 weeks after the last product application. The following clinical/instrumental evaluation was performed during the visit: clinical assessment of hip-abdomen adipose pannicula, circumference measurements, ultrasonographic evaluation of adipose pannicula thickness, and plicometry. At the end of treatment, the slimming activity of the study product resulted in clinically different results than placebo, determined by a significant decrease in abdomen/hips circumferences and considerable reduction of abdomen/hips adipose pannicula thickness. The tolerability of the product was good and the enrolled volunteers expressed their full satisfaction with the studied product. (*SKINmed.* 2015;13:23–29)

In our modern society, canons of beauty define "being beautiful" as having a slim and well-shaped figure. Most women who wish to conform to these standards aim to eliminate fat deposits in specific body areas.

Adipose tissue is a superficial layer of the subcutaneous tissue (or hypodermis). Its presence is normal in the human body. Subcutaneous fat deposits have various functions: from storing energy and insulating the body to having an aesthetic role of hiding bones and muscle protrusion. The quantity and distribution of subcutaneous fat deposits is extremely variable, depending on age, sex, genetic background, and diet.

This adipose tissue can accommodate volume variation, reaching up to 3 kg. It consists of fat lobules made of adipocytes (cells specialized in storing fat) and connective fibers. Life stimuli, eg, hormonal changes, physical activity (active such as gymnastic or passive such as massage) affect blood circulation and fat availability and, subsequently, the adipocytes size and distribution. Subcutaneous fat deposits are usually present in men and women in the tummy and hip areas.

Until the adipose tissue remains well supplied by the lymphatic and blood systems and the lobules remain of reasonable size, the fat tissue can be defined as healthy. The fat stored is readily available to body and cell metabolisms, responding to external or internal solicitations, either of a mechanical or chemical nature. This is not the case when cellulite is present: this typically feminine phenomenon, which can also be linked to hormonal changes, is a pathology linked to general tissue degeneration, which prevents the fat from being readily available.[1,4]

The advanced slimming product test was developed to fight the imperfections from the nonpathological form of localized fat deposits in the abdomen. Its formula is specifically designed to shape and slim the tummy and hip areas. The results of this treatment are not caused by slimming but by reshaping of the area as a result of a local reduction in subcutaneous fat deposits, possibly because this type of fat is intrinsically available for cell and body metabolisms.

The product contains many different actives with specific mechanisms of action. A specific complex that promotes lipolysis,

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contains vegetal extracts of Ficus carica bud processed with a slow-release polymer, *Gelidium cartilagineum*, *Fucus vesiculosus*, and *Sphacelaria scoparia*.

The first ingredient is an extract in glycerin and alcohol of *Ficus carica* buds, rich in flavonoids such as chlorogenic acid, which increases release of free fatty acids, thus reducing adipocyte size. Chlorogenic acids are cinnamic acid derivatives with biological effects mostly related to their antioxidant and antiinflammatory activities. The matrix of this delivery system provides a ready "reservoir" for the active ingredient, reducing any possible irritation of the molecules entrapted. It also enables maintaining the ingredient at effective levels for extended periods of time, providing for longer-lasting performance. The second active is an oily extract of *Gelidium cartilagineum*, a red seaweed rich in rodystherol (1.5% of active sterol). Sterols or derivatives, particularly active in the *Rhodophyta* are often used as a lipolytic and firming agent. The lipolytic activity is caused by the activation of the adenylate cyclase enzyme of the adipocyte membranes. The intracellular concentration of cyclic adenosine monophospate increases, activating the transformation of the triglycerides stored in the adipocytes into fatty acids and free glycerol.

Fucus vesiculosus was the original source of iodine, discovered in 1811, and was used extensively to treat goitre, a swelling of the thyroid gland related to iodine deficiency.

Primary chemical constituents of this plant include mucilage, algin, mannitol, beta-carotene, zeaxanthin, iodine, bromine, potassium, volatile oils, and many other minerals. The main use of bladder wrack (and other types of seaweed) in herbal medicine is as a source of iodine, an essential nutrient for the thyroid gland.

The complex is completed by *Sphacelaria scoparia* extract, which is derived from a special alga called sea broom that has been studied for its ability to inhibit the growth of fat cells. Adipocyte differentiation is inhibited by controlling the expression of fatty acid synthetase and stearoyl-CoA desaturase. Simultaneously, extracts of *Sphacelaria scoparia* help firm the skin by increasing collagens I and IV synthesis, thereby enhancing the skin's support properties.

The product also contains Buckwheat wax, an active ingredient useful in inhibiting or reducing lipogenesis. Buckwheat wax is a pale green wax with a characteristic odor that is obtained from the grains of *Polygonum fagopyrum* by means of a supercritical carbon dioxide extraction in the presence of a vegetable oil followed by the addition of a hydrogenated vegetable oil. Supercritical carbon dioxide offers the advantage of being inert, colorless, odorless, and nontoxic. This wax is rich in phytosterols, mainly β-sitosterol and campesterol, which inhibit lipogenesis. Stigmasterol does not display an effect on lipogenesis, but, on the other hand, it stimulates lipolysis. The effect obtained with Buckwheat wax is superior to that of the isolated phytosterols. Therefore, its inhibitory effect is likely associated with a cumulative effect of the phytosterols and/or an effect of other compounds, which promotes the effects of sterols such as unsaturated fatty acids.

Together with these natural plant extracts, the action "strategy" is also based on a cryothermal/vasomotor action performed by the presence of menthol, menthyl lactate, and ethyl nicotinate. This innovative mechanism caused by a rapid change of local temperature from hot to cold stimulates the subcutaneous microcirculation and elimination of excess liquid, helps to increase the receptiveness of the skin by enhancing the absorption of the active ingredients, and reactivates the metabolism responsible for the natural elimination of fat and cellulite.[5,8]

MATERIALS AND METHODS

A randomized controlled clinical trial vs placebo (double-blind study) was performed under dermatologic control for 4 weeks in 110 female healthy informed volunteers. A total of 55 participants were included in each of the two comparing groups, aged between 30 and 55 years, with a body mass index <30, presenting with light/moderate adipose pannicula at the level of the waist and hips (grade 1, 2, and 3 at the visual aspect according to the following score: 0=no fat deposition, 1=slight dimpling of the skin, 2=dimpling and skin depression, 3=dimpling and depressed striation, and 4=palpable nodules and depressed striations). At each visit, patient weight was recorded (variation range ±1.5 kg).

The study included an additional visit 4 weeks after the last product application. Volunteers were instructed to apply the product on the skin in an adequate quantity twice a day, followed by a light massage, until complete absorption.

All enrolled participants had no weight variations (±1.5 kg) during the last month before the beginning of the study and they accepted to not modify their eating habits or lifestyle (eg, physical activity and hypocaloric diets) during the study.

Five participants "dropped out" of the study for personal problems not related to the use of the tested products. Therefore, the study was completed in a total of 105 volunteers (52 for the product formulation and 53 for the placebo formulation)

The trial included the following visits: baseline (T0) before product use, an intermediate visit after 2 weeks of treatment (T2), end of product application after 4 weeks of treatment

(T4), and follow-up visit 4 weeks after the last product application (T8).

To determine the efficacy of the product under study, clinical-instrumental evaluations planned by the experimental procedure were carried out as follow: clinical assessment of hip-abdomen adipose pannicula on the basis of a visual score, waist circumference measurement at the level of the umbilicus, hip circumference at the level of the anterior iliac spine, and subgluteal circumference at the level of the subgluteal furrow. All measurements were performed under standard conditions with a specific electro-optical system equipped to align the volunteer's position. To reduce intra-individual variability, circumference measurements were performed three times for each level. The electro-optical system provides a definite and reproducible adjustment to the individual's position with a graduate panel positioned behind the back.

The system is composed of a vertical trace for the electro-optical system, a fixed horizontal bar, two-point lasers assembled on the fixed horizontal bar trough (a sliding system that allows for each one horizontal independent movement), and a graduated panel (mm scale) placed in front of the electro-optical system at a fixed distance that determines the coordinates.

To determine the coordinates of circumferences, the investigator located two levels on the abdomen (waist and iliac spine) and one level under the gluteal region. The investigator determined the panel alignment of the two laser projections: each laser touched the patient tangentially and produced a projection on the graduated panel. With a dermographic pen, the investigator marked the points on the patient's skin.

At every visit, ultrasonographic evaluation was performed monolaterally at the level of the abdomen (3 cm sidewards umbilicus) and adipose pannicula at the level of the hips (right or left side according to a defined randomization list). Ultrasonographic measurements of adipose panniculum thickness (mm) was performed with BodyMetrix BX 2000 (IntelaMetrix, Inc, Livermore, CA). The BX 2000 generates an ultrasound signal (1–10 MHz) that propagates through tissue and then records the reflected signal. Calculation of the thickness of a determined tissue is possible by measuring the time that the signal takes to reach an interface and multiplying it by the ultrasound speed in that specific tissue (for fat tissue, this speed is approximately 1400 m/s).[9,13]

To measure the thickness of the hip adipose fold, plicometry was also performed. The skin-fold caliper is an instrument that measures, with a pressure of 10 g/mm^2, the thickness of a skin tissue layer with its substratum of body fat.[11]

All measurements were performed under standard environmental conditions (temperature 22±2°C, relative humidity <60%). Before each visit, the volunteer was acclimatized under relax conditions for at least 10 to 15 minutes. The evaluations were preformed after 10 hours of the last application.

The cosmetic acceptability of both formulations (product and placebo) at the end of the study was evaluated by the volunteers and the products' efficacy and tolerance by the volunteers and the investigators.

STATISTICAL ANALYSIS

Data from the five patients who dropped out of the study and one other volunteer were excluded from statistical analysis because of protocol violation (body weight increase form T2 >1.5 kg); therefore, analysis was carried out on blinded data of 52 patients for each study group. Data processing was performed as follows: (1) evaluation of each study product vs basal condition (Friedmann test followed, in case of statistical significance, by Dunnett test for clinical evaluations; analysis of variance followed, in case of statistical significance, by Dunnett test for the instrumental evaluations); and (2) comparison product formulation vs placebo formulation time by time (Wilcoxon test for clinical evaluations and Student t test for instrumental evaluations).

RESULTS AND DISCUSSION

The activity of the tested product is expressed in absolute values and in comparison to the placebo. Morphometric evaluations underlined the "slimming" activity of the study product formulation. After 2 weeks of application (T2), mean values of the circumferences were statistically reduced (Dunnett test $P<.05$) when compared with baseline (T0). No statistically or clinically appreciable variation of morphometric assessment was shown with placebo. Results (circumferences mean value and reduction) are summarized in Table I and Figure 1.

Ultrasonographic measurement of adipose pannicula performed monolaterally at the level of the abdomen (3 cm sidewards umbilicus) and hips showed a statistically (Dunnett test P<.05 vs T0) and clinically significant reduction of panniculum thickness (mm) of 7.3% for the abdomen and 20% for the hip after 4-week treatment (T4), corresponding to an average decrease of 1.71 mm and 2.5 mm, respectively. Moreover, after 4 weeks of treatment, the "lipo-reducing" activity in the hip panniculum of the tested product was statistically different than the placebo (Student t test $P<.05$ $T4_{product}$ vs $T4_{placebo}$). Although 4 weeks after the last product application (T8), no statistically significant difference between study products was found, the abdomen and

Table I. Circumference Measurements and Reduction

		T0	T2	T2–T0	T4	T4–T0	T8	T8–T0
Product	First level (waist)	86.2	85.2	–1.0[a]	84.1	–2.1[a]	84.2	–2.0[a]
	Second level (iliac spine)	94.3	93.5	–0.8[a]	92.1	–2.2[a]	92.6	–1.7[a]
	Third level (under gluteus)	98.8	97.8	–1.0[a]	96.9	–1.9[a]	97.2	–1.6[a]
Placebo	First level (waist)	85.1	85.0	–0.1	85.1	0	85.1	0
	Second level (iliac spine)	92.9	92.9	0	92.8	–0.1	92.7	–0.2
	Third level (under gluteus)	98	98	0	97.8	–0.2	97.8	–0.2

Abbreviations: T2, after 2 weeks of treatment; T4, after 4 weeks of treatment; T8, 4 weeks after end of treatment.
[a]Dunnet test, $P<.05$ vs baseline (T0).
Values are expressed in centimeters.

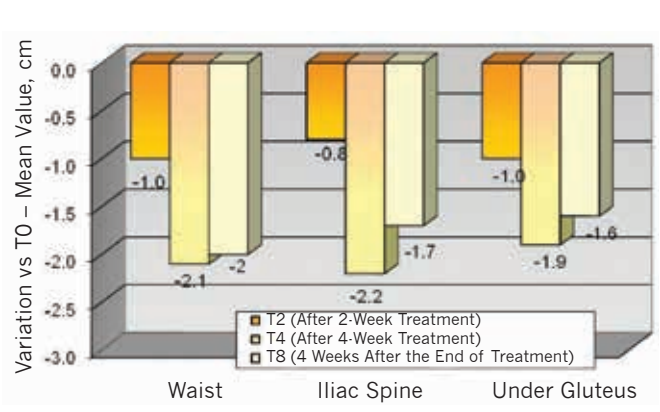

Figure 1. Circumference measurements variation vs baseline after product administration.

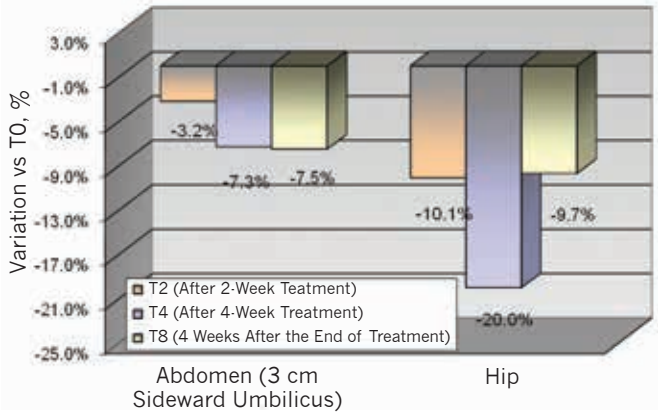

Figure 2. Ultrasonographic assessment variation percentage vs baseline after product administration.

hip pannicula thickness reduction results yet marked (–7.5% vs T0 corresponding to an average decrease of 1.76 mm for the abdomen and –9.7% vs T0, corresponding to an average decrease of 1.21 mm for the hip), index of a "long-lasting" activity of the "active" formulation (Table II, Figure 2).

Measurement of the patients' skin fold performed monolaterally (left or right side) at the level of the hips, highlighted after 2-week treatment (T2), showed a statistically significant reduction (Dunnett test $P<.05$ T2 vs T0) in adipose pannicula thickness of 1.24 mm (mean value) corresponding to a reduction percentage vs T0 of 6.5%. At T4, this percentage was even more marked (–10.8% with an average decrease of 2.08 mm) and statistically different than placebo (Student t test $P<.05$ $T4_{product}$ vs $T4_{placebo}$). The product activity was present at T8 (Dunnett test $P<.05$ T8 vs T0 and Student t test $P<.05$ $T8_{product}$ vs $T8_{placebo}$) (Table III, Figure 3).

CLINICAL ASSESSMENT

Clinical assessment of hip and abdomen adipose pannicula was performed using the following visual scoring: 0: no visible pannicula; 1: presence of reduced pannicula (light grade); 2: presence of medium pannicula (light-moderate grade); 3: presence of relevant pannicula (moderate grade); and 4: very relevant pannicula (severe grade).

At the end of treatment (T4), the product resulted in a statistically significant reduction in hip adipose pannicula visual score

Table II. Ultrasonographic Measurements and Reduction

		T0	T2	T2–T0	T4	T4–T0	T8	T8–T0
Product	Abdomen (3 cm sideward umbilicus)	23.38	22.64	–3.2% –0.74 mm	21.67	–7.3% –1.71 mm[a]	21.62	–7.5% –1.76 mm[a]
	Hips (iliac spine)	12.46	11.20	–10.1% –1.25 mm[a]	9.96	–20% –2.49 mm[a,b]	11.25	–9.7% –1.21 mm[a]
Placebo	Abdomen (3 cm sideward umbilicus)	24.07	24.53	+0.46 mm	24.46	+0.39 mm	23.99	–0.08 mm
	Hips (iliac spine)	11.28	11.53	+0.25 mm	11.90	+0.62 mm	11.89	+0.61 mm

Abbreviations: T2, after 2 weeks of treatment; T4, after 4 weeks of treatment; T8, 4 weeks after end of treatment.
[a]Dunnet test, $P<.05$ vs baseline (T0).
[b]Student t test, $P<.05$ $T4_{product}$ vs $T4_{placebo}$.

Table III. Plicometry Measurements and Reduction

		T0	T2	T2–T0	T4	T4–T0	T8	T8–T0
Product	Hips (iliac spine)	19.19	17.95	–6.5% –1.24 mm[a]	17.11	–10.8% –2.08mm [a,b]	17.57	–8.4% –1.62 mm[a,c]
Placebo		20.13	20.13	0	20.04	–0.09 mm	20.15	+0.02 mm

Abbreviations: T2, after 2 weeks of treatment; T4, after 4 weeks of treatment; T8, 4 weeks after end of treatment.
[a]Dunnet test, $P<.05$ vs baseline (T0).
[b]Student t test, $P<.05$ $T4_{product}$ vs $T4_{placebo}$.
[c]Student t test, $P<.05$ $T8_{product}$ vs $T8_{placebo}$.

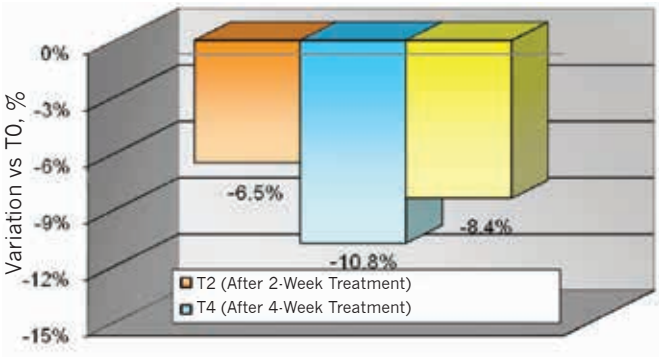

Figure 3. Percentage of skinfold caliper variation vs baseline after product administration.

compared with that at baseline (Dunnett test $P<.05$ T4 vs T0). The score improved at least one grade in 56% of treated patients. Four weeks after the last product application, this percentage was still clinically consistent (score improved at least one grade in 46% of volunteers) and statistically significant compared with baseline (Figure 4 and Figure 5).

Product activity was also statistically significant compared with placebo at T4 and at T8 (Wilcoxon test $P<.001$ $T4_{product}$ vs $T4_{placebo}$ Wilcoxon test $P<.01$ $T8_{product}$ vs $T8_{placebo}$).

SELF-EVALUATION QUESTIONNAIRE

Product efficacy on adipose pannicula was noted by 50% of volunteers (37% medium and 13% marked) at the level of the abdomen and by 51% (35% medium, 12% marked, and 4% very marked) at the level of the hips. Moreover, 42% (29% medium and 13% marked) of the participants observed a reduction in waist circumference, 70% (35% medium, 33% marked, and 2% very marked) an improvement in skin smoothness, and 60% (33% medium, 21% marked, and 6% very marked) in skin tonicity. The majority of patients (63%) in the placebo

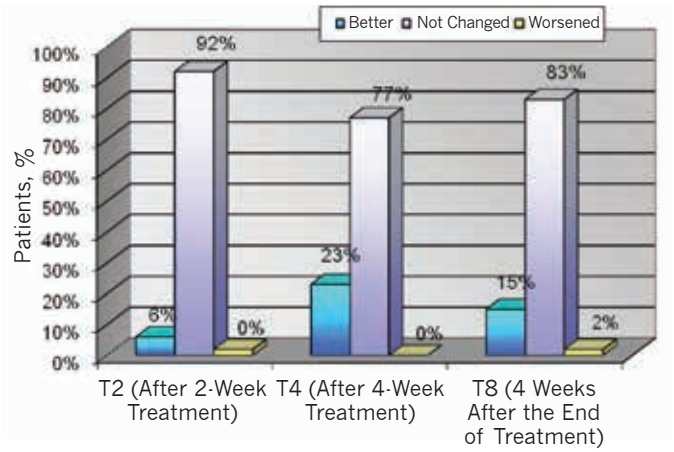

Figure 4. Clinical evaluation of abdomen adipose pannicula variation vs baseline after product administration.

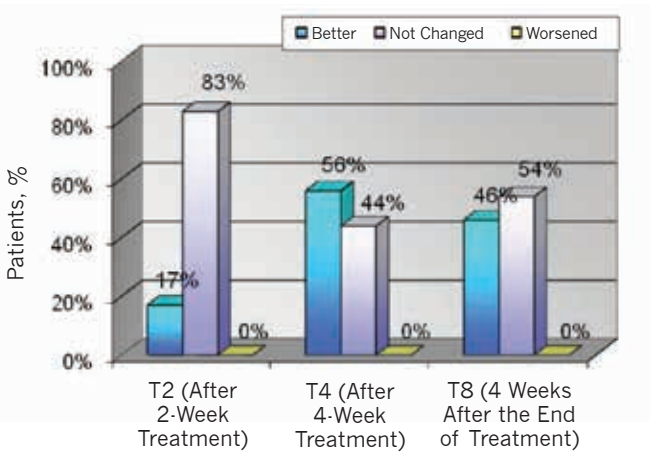

Figure 5. Clinical evaluation of hip adipose pannicula variation vs baseline after product administration.

group noted an improvement in skin smoothness (33% medium, 26% marked, and 4% very marked) but did not report any slimming activity.

The investigator's efficacy judgment at T4 and T8 confirmed the above-mentioned results. No adverse events/reactions related to the study products occurred during the trial. The patients reported the tolerability of both products as good/excellent (100%) as confirmed by the investigator's final tolerability evaluation performed at the end of the treatment period.

The cosmetic acceptability of the product was generally good. In particular, at the end of the treatment period (T4), a high percentage of volunteers appreciated product color (good-excellent = 83%), perfume (good-excellent = 67.5%), consistency (good-excellent = 90%), spreadability (good-excellent = 90%), absorption (good-excellent = 67%), effect on the skin (warm/cold sensation; good-excellent = 61.5%), and absence of greasiness (good-excellent = 71%), and of residues on the skin after application (good-excellent = 79%).

DISCUSSION

Localized adiposity is a cutaneous phenomenon that appears as a result of a morphological change in subcutaneous adipose tissue. This change is characterized by an increase in adipocyte size caused by a high intake and storage of lipids in some well-defined body zones. Several factors have an influence on this process, including hormonal variations and sedentary and unhealthy lifestyle. Enlarged adipocytes are less receptive to hormonal and sympathetic adrenergic stimuli. In light to moderate adiposity, the tissue is reactive and responds well to stimuli such as physical activity and cosmetic and aesthetic treatments (eg, massage) aimed at mobilizing adipose accumulations and draining excess liquid.

The slimming effect obtained with cosmetic products comes from the improvement of the skin's unsightly appearance associated with localized adiposity because they activate the cellular catabolic processes leading to intracellular lipid hydrolysis into free fatty acids. These are then released into the blood circulation and carried to the various tissues, particularly muscles, where energy is produced in the form of ATP via oxidation.

CONCLUSIONS

The present findings support the efficacy of a market-available slimming treatment. In particular, the slimming effect was demonstrated in the abdomen and hip circumference and pannicula adipose thickness. After only 2 weeks of treatment and more consistently at the end of the study, the product produced a significant decrease in abdomen/hip circumferences and a considerable reduction in abdomen/hip adipose pannicula thickness. The product's slimming activity resulted in clinically different results than placebo, which, after massage repeated twice a day for 4 weeks, was not able to produce any considerable reduction in abdomen and hip adipose pannicula. Moreover, contrary to the findings in the placebo group, the majority of participants using the product noted its lipo-reducing activity. The positive results were still present 4 weeks after the last product application, an index of a "long-lasting lipo-reducing" activity of the tested formulation. These results were found in the absence of significant changes in body weight. The present slimming formulation is based on the biological activity of different compounds: an extract of *Ficus carica* buds, which increases free fatty

acid release that reduces adipocyte size; an oily extract of *Gelidium cartilagineum*, rich in rodystherol, in which lipolytic activity is caused by activation of the adenylate cyclase enzyme of the adipocyte membranes; *Fucus vesiculosus* source of iodine; *Sphacelaria scoparia* extract, which inhibits the growth of fat cells; and Buckwheat wax, an active ingredient useful in inhibiting or reducing lipogenesis. This formulation, which includes different compounds, did not show any adverse dermatologic events during treatment and is associated with good to excellent cosmetic acceptability. The present study reports the clinical effectiveness and patient satisfaction of a slimming treatment specifically targeting the stomach and hips.

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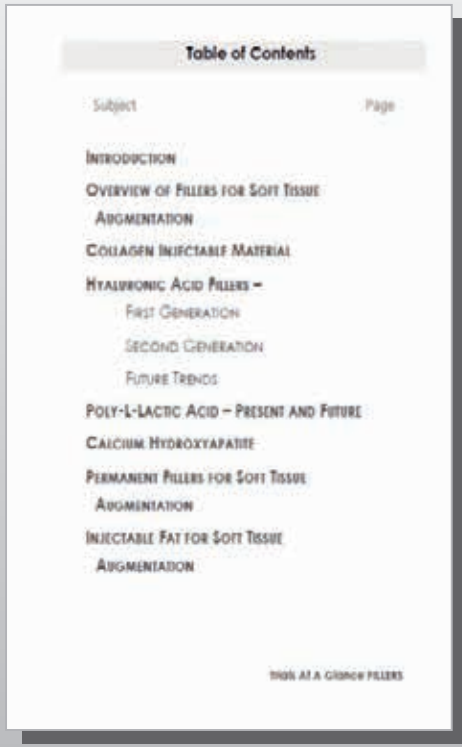
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Injectable Fat for Soft Tissue Augmentation


A Prospective, Split-Face, Randomized, Comparative Study of Safety and 12-Month Longevity of Three Hyaluronic Acid Dermal Fillers for Treatment of Nasolabial Folds

Authors: Prager W, Wissmuller E, Havermann I, Bee EK, Howell DJ, Zadrobilek I, Simon J

Reference: Dermatol Surg 2012; 38:1143-1150

Disease: Skin Rejuvenation, Wrinkles

Device: Belotero Basic (HA-1), Restylane (HA-2), Juvederm Ultra 3 (HA-3)

Purpose: To evaluate, in a prospective, split-face, randomized, two-armed study the long-term effectiveness and safety of three common HA products used in facial practice

Design: Prospective, split-face, randomized, two-armed

Patients: 40 patients

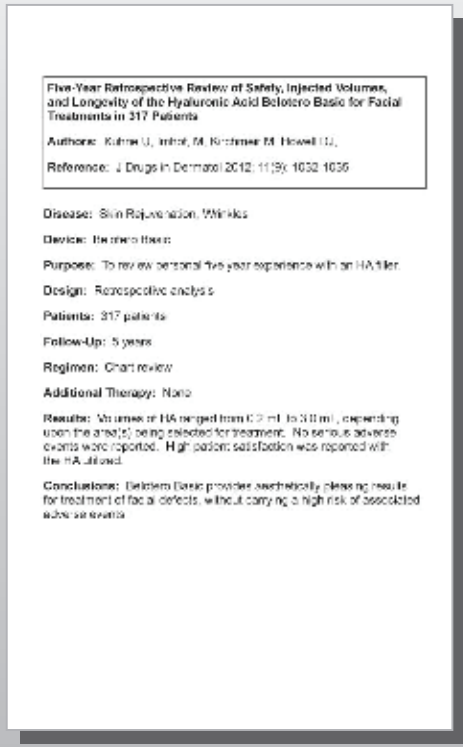
Follow-Up: 12 months

Regimen: Arm A – 20 patients received HA-1 in one NL fold and HA-2 in the other; repeated for Arm 2 with HA-1 and HA-3.

Additional Therapy: None

Results: Adverse events were considered similar between treatment groups. Mean pretreatment NLF severity rating for both arms was 2.3; at 12 months, mean severity rating was 1.0 for Arm A and 1.0 for Arm B. Although not statistically different, participants tended to show a preference for HA-1.

Conclusions: All three HAs provided equivalent results.


Five-Year Retrospective Review of Safety, Injected Volumes, and Longevity of the Hyaluronic Acid Belotero Basic for Facial Treatments in 317 Patients

Authors: Kuhne U, Imhof, M, Kirchner M, Howell DJ,

Reference: J Drugs in Dermatol 2012; 11(9): 1032-1036

Disease: Skin Rejuvenation, Wrinkles

Device: Belotero Basic

Purpose: To review personal five-year experience with an HA filler

Design: Retrospective analysis

Patients: 317 patients

Follow-Up: 5 years

Regimen: Chart review

Additional Therapy: None

Results: Volumes of HA ranged from 0.3 mL to 3.0 mL, depending upon the area[s] being selected for treatment. No serious adverse events were reported. High patient satisfaction was reported with the HA utilized.

Conclusions: Belotero Basic provides aesthetically pleasing results for treatment of facial defects, without carrying a high risk of associated adverse events

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REVIEW

The Use of Traditional Chinese Medicine in Some Dermatologic Diseases: Part I—Acne, Psoriasis, and Atopic Dermatitis

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ABSTRACT

Traditional Chinese medicine (TCM) is increasingly being used in the Western world particularly in specialty areas such as gynecology, pediatrics, nutrition, and dermatology. TCM is an alternative method of therapy that proposes to treat symptoms that Western medicine is unable to manage by treating the underlying causes of disease. The authors provide a general overview of TCM remedies used in the treatment of various dermatologic disorders (acne, psoriasis, atopic dermatitis) for dermatologists interested in this unconventional therapeutic approach. (*SKINmed.* 2014;12:32–38)

From the beginnings of Chinese medicine, more than 4000 years ago, the theories on the causes of diseases and their treatments have greatly evolved.[1,2] The use of traditional Chinese medicine (TCM) methods is becoming more widespread in the Western world, especially for certain specialty areas such as gynecology, pediatrics, dietetics, and dermatology. Of interest is that patients appear to be more receptive to TCM, so that the knowledge of methods, herbs or substances used, their mechanisms of action, and their side effects cannot be overlooked by Western clinicians. Furthermore, even if most practitioners have no intention of using TCM in their professional work, they should be trained to identify the effects associated with these drugs.[3,4]

TCM represents an alternative method of therapy, which proposes to ameliorate or heal those symptoms that Western medicine is unable to cure, by treating the underlying causes of disease. According to TCM, most skin conditions do not respond favorably to Western medical interventions because they are aimed at treating only the symptoms and not the causes of diseases. TCM argues that skin disorders arise from a number of other disturbances, such as excesive heat in the body, poor digestion, bad circulation, stagnation of energy, and emotional or hormonal problems. Moreover, TCM works by regulation of either body energy or meridian system ('*qi*, 氣'), because if there is an energy blockage in our body or in meridians, disease will develop. A TCM treatment protocol might include a combination of acupuncture; Chinese herbs in raw, tincture, or pill form; external herbal washes or creams; and dietary suggestions that would reestablish the balance of Yin (陰, *yīn*) and Yang (陽, *yáng*), returning the body to a healthy state.[1–4]

For TCM, diet plays an important role because dietary imbalance can negatively influence the organs and the *qi*. Foods can be divided into hot (stimulating, or yang) and cool (calming, or yin) forms. Therefore, overstimulated individuals may benefit from foods that are considered yin; conversely, those who have a yang-deficient condition may feel well with a more stimulating yang diet[1–4] (Table I).

Some studies published in international literature have shown the usefulness of TCM in the treatment of certain skin disorders, in particular acne, flushing of face, rosacea, and itching disorders such as eczema and psoriasis.

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Table I. Calming and Stimulating Foods According to Traditional Chinese Medicine

YIN Foods (calming)	YANG Foods (stimulating)
Abalone	Artichoke
Agar	Basil
Banana	Black tea
Barley	Butter
Beer	Butterfish
Bran	Cayenne
Buckwheat	Cherries
Cottage cheese	Chestnuts
Crab	Chicken
Cucumber	Chili
Egg white	Cinnamon
Frog's legs	Chives
Gluten	Coconut
Kelp	Coconut milk
Lettuce	Cod
Lotus root	Coffee
Malt	Coriander
Mango	Dates
Marrow	Egg yolk
Melon	Fennel
Millet	Green onion
Mushrooms	Ham
Octopus	Lamb
Oysters	Malt
Pears	Mussels
Peas	Mustard
Persimmons	Nectarine
Pumpkin	Olives
Rabbit	Oolong tea
Rock salt	Peach
Seaweed	Pepper
Sesame oil	Pine nut
Snails	Safflower
Sugar, cane	Shrimp
Summer squash	Soy oil
Sunflower seeds	Sugar, brown
Tangerine	Sweet potato
Tea, green	Turmeric
Tofu	Vinegar
Tomato	Wine
Wheat	
White fungus	

On the wake of public scientific papers from China and Western literature that elucidate numerous TCM therapies, we propose to provide a better knowledge and general overview of TCMs used in the treatment of some dermatologic disorders, including acne, psoriasis, and atopic dermatitis. Autoimmune bullous disorders and lichen planus will be discussed in Part II.

ACNE

Acne is a common cutaneous disease marked by inflamed and/or noninflamed eruptions of comedones, papules, pustules, nodules, or cysts, especially on the face, chest, and back, caused by alterations of pilo-sebaceous follicles.[5–7] The most common Chinese name for acne vulgaris is *fen ci*, meaning white thorns. This denomination indicates the protruding shape of whiteheads.[8]

According to TCM, conflicting with Western daily treatments that never address the problem, acne is a symptom of internal heat and dampness: the heat triggers acne activity, where bacteria thrive in the damp body environment. The red color of acne lesions indicates the existence of heat evils, while the white matter and pus inside the lesions indicate dampness and phlegm. Among sources of body heat are stress, overconsumption of stimulating foods, hormonal activity, blood insufficient to clean toxins, agitated thoughts, atmospheric heat, and constraint of *qi*. Common causes of dampness in the body are water accumulation for weak digestion; oily, fatty, cold, or raw foods; irregular eating habits; insufficient sweating; and overly damp environment.[8]

TCM differentiates several types of heat that can cause acne: lung heat, stomach heat, blood heat, yoxic heat, and damp heat. Each type creates a distinct pattern of symptoms that require a specific treatment. Acne is most often caused by heat in the lung and stomach meridians. The lung meridian starts in the middle of the body and moves up to the chest. The stomach meridian starts at the face and goes through the chest.[8]

The heat in the lungs and stomach will present as acne that is mainly on the face, with oily or shiny skin. Patients with this kind of pattern might also have a dry mouth and feel thirsty and may have constipation and dark urine. Their tongue is often red and their pulse rate rapid. The treatment principle is to clear the heat: Pi Pa Qing Fei Ying (Table IIA) and Dan Di Tang (Table IIB) may be used for heat in the lungs and in the stomach, respectively.[8]

Acne caused by stagnation of phlegm, dampness, and blood as dark red and appears in clusters. The sores will also be quite long-lasting. The treatment principle here is to activate blood circulation, using herbal medicines such as Tao Hong Si Wu Tang (Table III).[8]

The acne caused by toxic heat is similar to acne caused by blood heat but is more severe, filled with pus. Wu Wei Xiao Du Yin Jia Wei (Table IV) may be used to clear heat and resolve toxins.[8] Moreover, based on the strength of different symptoms, the herbal medicine recipes may be modified with the subtraction or addition of herbs.[8]

Table IIA. Composition of Pi Pa Qing Fei Ying

Pi Pa Ye (*Folium Eriobotryae*), Sang Bai Pi (*Cortex Mori*), Huang Bai (*Cortex Phellodendri*), Huang Lian (*Rhizoma Coptidis*), uncooked Gan Cao (*Radix Glycyrrhizae*), and Ren Shen (*Radix Ginseng*).

Table IIB. Composition of Dan Di Tang

Dan Shen (*Radix Salviae Miltiorrhizae*), Sheng Di (uncooked *Radix Rehmanniae*), Gan Cao (*Radix Glycyrrhizae*), Hu Zhan (*Rhizoma Polygoni Cuspidati*), and Da Huang (*Radix Et Rhizoma Rhei*).

Table III. Composition of Tao Hong Si Wu Tang

Dang Gui (*Radix Angelicae Sinensis*), Chi Shao (*Radix Paeoniae Rubrae*), Sheng Di (uncooked *Radix Rehmanniae*), Chuan Xiong (*Rhizoma Chuanxiong*), Tao Ren (*Semen Persicae*), and Hong Hua (*Flos Carthami*).

Table IV. Composition of Wu Wei Xiao Du Yin Jia Wei

Zi Hua Di Ding (*Herba Violae*), Ye Ju Hua (*Flos Chrysanthemi Indici*), Lian Qiao (*Fructus Forsythiae*), Sheng Di (uncooked *Radix Rehmanniae*), Chi Shao (*Radix Paeoniae Rubrae*), Huang Qin (*Radix Scutellariae*), Dan Pi (*Cortex Moutan*), Ju He (*Semen Citri Reticulate*), Pi Pa Ye (*Folium Eriobotryae*), and Jie Geng (*Radix Platycodi*).

The single herb can exercise a prevalent antimicrobial, anti-inflammation, or anticomedogenic effect. Antimicrobial herbs are likely to play a role against *Propionibacterium acnes* and *Staphylococcus epidermidis*, which are involved in the pathogenesis of acne. The best supported natural treatment in this regard is a formulation of powdered extracts of 17 Kampo crude drugs, the Keigai-rengyo-to, which shows a strong antibacterial activity towards *P acnes*.[9,10] A Japanese study comparing the effects of Keingai-rengyo-to with minocycline on P acnes showed that the minocycline had anti-lipase activity at a low minimal inhibitory concentration (MIC), while the effects of Keingai-rengyo-to were insignificant.[11] Among the herbs with a prevalent anti-inflammatory action, there is the *Scutellaria* root extract. The potential for systemic and topical administration of this herb to help patients with acne is great, although clinical trials are unfortunately lacking.[12]

Another study showed that Dang Gui (*Radix Angelicae Sinensis*) has a suppressing effect on neutrophil chemotaxis while Huang Lian (*Rhizoma Coptidis*) and Gan Cao (*Radix Glycyrrhizae*) have remarkable antibacterial activity against *P acnes*.[13] Moreover, a clinical study on 86 cases of acne vulgaris treated with Fu Fang She She Cao He Ji (compound oldenlandis mixture) showed that the herbal medicine is a promising agent for acne management.[14] TCM uses herbal medicines to stabilize the hormonal imbalance that can cause acne. The most interesting study on the matter has observed the effect of modified Longdan Xiegan Decoction on hyperandrogenism in patients with polycystic ovary syndrome (PCOS) of stagnant fire in Gan channel type. After treatment, the condition of menstrual disorder, acne, hirsuitism, and serum levels of hormones were significantly improved.[15] Another clinical study on the effect of Bushen Huayu Qutan (BHQR, a Chinese recipe formulated to resolve stasis and to dispell phlegm) in treating PCOS has showed that BHQR could not only significantly relieve the symptoms and signs in patients with PCOS, but also regulate their ovarian function.[16] These results were confirmed by a study performed on rats, according to which the effects of BHQR on balancing the internal environment of ovaries may be caused by the reduction in serum insulin level and decrease in the expressions of ovarian inhibin, insulin-like growth factor-I, and vascular endothelial growth factor.[17]

In addition to herbal medicines, TCM offers many other remedies for acne, including diet modification, acupuncture, cupping, and moxibustion therapy.

From the perspective of the Chinese medical theory, an unhealthy diet is considered one of the causes of imbalance in our body. During acne treatments, Chinese physicians, in contrast to their Western counterparts, generally recommend a strict *yin* or *yang* dietary program (Table I). Using the TCM approach, a group of Chinese and French clinicians have found an association between acne and certain foods in contrast to previous studies, which calls for further researches on the subject.[18]

Acupuncture is an alternative medicine methodology that originated in ancient China that treats patients by manipulating thin, solid needles which are inserted at acupuncture points into the skin. According to TCM, stimulation of these points can correct imbalances in the flow of *qi* through channels known as meridians.[19] Cupping therapy is also an ancient practice that consists of creating a local suction on the skin. Practitioners believe that this technique mobilizes blood flow in order to promote healing. Suction is created using heat (fire) or mechanical devices (hand or electrical pumps).[20] Moxibustion is a form of fire heat treatment that stimulates specific acupuncture points of the body. The procedure consists of placing a small, cone-shaped stick of *Artemisia vulgaris* (a spongy herb commonly known as mugwort) on top of an acupuncture point, burning on the skin[21]; however, Western scientific research has not found any significance associated with these three practices.

Acupuncture therapy is considered by TCM to be an effective treatment in reducing the cycle of acne development. It works by regulating hormones, decreasing inflammation, and reducing infection.[22] Similar results are also obtained with cupping and moxibustion treatments.[20,21] Some clinical studies conclude that acupuncture, moxibustion, and cupping therapies are safe and effective and combined acupuncture-moxibustion therapy or acupuncture-cupping therapy are better than single acupuncture/moxybustion/cupping therapy.[23,24,25]

PSORIASIS

Psoriasis is an immune-mediated skin disorder that affects up to 3% of the world's population.[26] It is a chronic disease with no definitive cure available. As a result of the failure of conventional treatments, patients sometimes turn to alternative or complementary medicine, in particular TCM.[27]

According to TCM, psoriasis should be classified into 3 different types: blood heat syndrome, blood dryness syndrome, and blood stasis syndrome, in relation to the features of the disease and its course.[28–30] In Chinese literature, more than 174 herbs are reported to be effective in the treatment of psoriasis, although only a few controlled studies have been published in Western literature.[27]

The most commonly used herbs for psoriasis include *Rehmania glutinosa*, *Angelica sinensis*, *Salvia miltiorrhiza*, *Dictammus dasycarpus*, *Smilax glabra*, *Oldelandia diffusa*, *Lithospermum erythrorhizon*, *Carthamus tinctorius*, *Glycyrrhiza uralensis*, *Indigo Naturalis*, and Weng-tong-hua-yu.[27,31,32]

Rehmania glutinosa is effective in the blood heat type of psoriasis.; its effects include clearing heat, cooling blood, nourishing Yin, and promoting the formation of body fluid. Its biological effect would be related to the property of inhibiting the release of histamine and tumor necrosis factor α (TNF-α) or interleukin (IL) 1 secretion from mouse astrocytes.[27,33]

Angelica sinensis corrects deficiency, activates and replenishes blood and, according to TCM, has been proven to increase IL-2 secretion in vitro.[34] This datum is in contrast with its anti-inflammatory effect and worsens psoriasis.[34] Further studies are needed to better clarify this point.

Salvia miltiorrhiza is thought to activate blood, eliminate blood stasis, and calm the mind. Laboratory studies demonstrated its effect on inhibition of carrageenin-induced rat paw edema, neutrophil chemotaxis, and reduction of interferony-γ and IL-12.[35–39]

The herb *Dictammus dasycarpus* clears heat, dries dampness, and repels wind. In the laboratory, it selectively inhibits delayed-type hypersensitivity (DTH).[40] Moreover, it has an hepatoprotective effect, which explains its frequent use in combination with other herbs that cause hepatotoxicity.[27]

Smilax glabra and *Oldelandia diffusa* are useful to clear heat, remove dampness, and detoxify body pathogens. While *S glabra* inhibits DTH and reduces carrageenin-induced edema,[27] *O diffusa* has a negative effect on psoriasis by increasing production of IL-6 and TNF-α.41

Lithospermum erythrorhizon cools blood, activates blood, detoxifies pathogens in the body, and clears internal heat. It is currently used in combination with other herbs such as *Glycyrrhiza*, *Ginseng radix, Angelicae radix, Houttuyniae berba, Astragali radix, Cnidii thizoma*, and *Coicis semen*. This mixture, called Shi-Ka-Ron, has been shown to completely suppress the production of IL-1α and TNF-α in mouse macrophages.[42] *L erythrorhizon* would also have an effect on TNF-α–induced angiogenesis.[43]

Carthamus tinctorius activates blood, removes blood stasis, relieves pain, and opens up blocked meridians. In mice it has been shown to inhibit inflammation.[44]

Glycyrrhiza uralensis has effects on strengthening *qi*, clearing heat phlegm, and relieving pain. It is considered a harmonizing herb, and therefore it is used in combination with other herbs to reduce their side effects and pungent taste. In the laboratory it has been shown to possess either immunosuppressive or immune-enhancing activities, depending on the circumstances.[45]

Indigo Naturalis is a dark blue powder derived from the leaves of plants such as *Baphicavatus cusia, Polygonum tinctorium, Isatis indigotica*, and *Indigofera tinctoria. Indigo Naturalis*' ability to modify the proliferation and differentiation of keratinocytes accounts for its application in the treatment of psoriatic patients.[31] A recent paper reported significant improvement in psoriatic plaques after 12 weeks of treatment with *Indigo Naturalis*.[46]

In a randomized placebo-controlled study, investigators compared the efficacy and safety of methotrexate with a formulation of Weng-tong-hua-yu in the treatment of chronic plaque psoriasis involving >20% of body surface area.[32] This study demonstrated that the TCM regimen is ineffective in the management of moderate to severe psoriasis. Further controlled studies are necessary to clarify whether these herbs are effective and, if so, standardize the dosages and their formulation.

ATOPIC DERMATITIS

Atopic dermatitis (AD) represents a chronic recalcitrant inflammatory dermatosis that typically appears in childhood, although onset of AD in adults is not uncommon. Its pathogenesis is complex and hinged on an interaction between susceptible genes, such as that of filaggrin, immunological factors, defects of skin barrier, infections, and neuroendocrine and environmental factors.[47–50] No definitive cure for AD exists, even if emollients, topical corticosteroids, and immunomodulating antimicrobial agents have been demonstrated to be quite effective in AD.[48,51,52]

Because these therapies are not satisfactory for many patients, seeking alternative treatments, including TCM, is increasing. Although Chinese literature supports the use of herbs in treating AD, Western literature lacks convincing results on the effectiveness of these treatments, because only a few controlled trials have been published on this topic.[53]

According to TCM, the main pathogenetic mechanisms of AD are wind, dampness, and heat. Recently, investigators reviewed trials on TCM in the treatment of AD, focusing attention on Zemphyte, PentaHerbs, Shuangfujun, and Hochu-ekki-to.[53]

Zemphyte (Phytopharm Plc, United Kingdom) is a decoction considered effective for AD since the past century.[54,55] Two different trials performed in the United Kingdom and Hong Kong showed opposing results. In fact, one demonstrated the superiority of this treatment by comparing it with placebo in both in children and adults,[54,55] while the other did not confirm these data, failing to demonstrate the real usefulness of this alternative therapy.[56]

PentaHerbs capsules were packaged and labeled by the Chinese Medicine Industry Centre (the Hong Kong Institute of Vocation Education) and their composition was standardized: 2 g of *Flos lonicerae* (Jinyinhua), 1 g of *Herba menthae* (Bohe), 2 g of *Cortex moutan* (Danpi), 2 g of *Rhizoma atractylodis* (Cangzhu), and 2 g of *Cortex phellodendri* (Huangbai).[53] Investigators demonstrated that PentaHerbs significantly improved Scoring Atopic Dermatitis values in children treated for 4 months.[57] In a subsequent double-blinded, randomized, placebo-controlled trial, investigators concluded that the PentaHerbs formulation is effective in improving quality of life and reducing topical corticosteroid use in children with moderate to severe AD.[58] Moreover, laboratory studies have demonstrated that PentaHerbs inhibits IL-4–induced CD23 expression on peripheral blood monocytes up to 60%.[59] Investigators found that PentaHerbs has in vitro and in vivo immunomodulation effects that might mediate the clinical efficacy observed in AD.[60]

Table V. Composition of Hochu-ekki-to

Radix astragali, Panax ginseng C.A. Mey, Rhizoma atractyloidis macrocephalae, Glycyrrhiza uralensis, Angelica sinensis, Citri reticulatae pericarpium, Rhizoma cimicifugae, Radix bupleuri, Zingiber officinale roscoe, and *Fructus jujubae date.*

Shuangfujun, compared with saline solution, boric acid, and Pifukang lotion, has been proven to be effective in improving and treating symptoms of AD.[61]

Hochu-ekki-to is a TCM formula consisting of 10 herbs (Table V) considered effective for patients with *Kikyo* (delicate, easily fatigable, or hypersensitivity condition).

A placebo-controlled study demonstrated that Hochu-ekki-to was a useful adjuvant therapy to conventional treatments for AD, permitting the reduction of topical corticosteroids and/or tacrolimus dosages.[62] In the literature there is a plethora of case series and anecdotal reports on the effectiveness of the herbal medicine or combination of herbs with acupuncture in AD, but evidence-based confirmation is still lacking.

CONCLUSIONS

Over the centuries, TCM and Western medicine have traveled along parallel lines with no opportunity to collaborate. In the recent decades, an interest in TCM has been growing among Western clinicians, progress has been made in the comprehension of pathogenic mechanisms of skin disorders, and the communication between Western and Eastern medicines has become more and more intensive. In the future, controlled studies aimed at evaluating the usefulness of TCM in dermatologic disorders and the foundations of its pharmacokinetics should be carried out. With the guidance from clinicians, it is likely that important discoveries will result from these studies.

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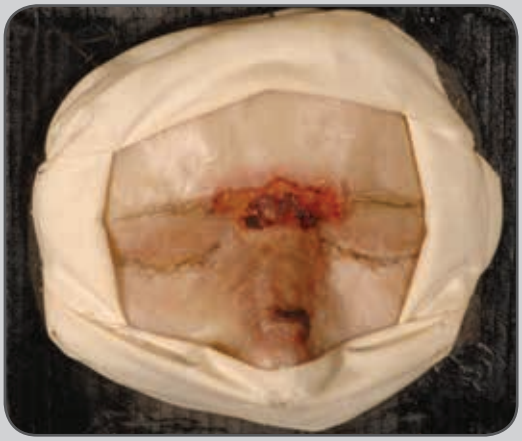

"**Ca baso**". Moulage No. 535, made by Lotte Volger in 1927 in the Clinic for Dermatology Zurich. Museum of Wax Moulages Zurich, www.moulagen.ch

Courtesy of Michael Geiges, MD

SELF ASSESSMENT EXAMINATION

W. Clark Lambert, MD, PhD

IInstructions: Please respond to each question as directed.

1. The origin of Traditional Chinese Medicine occurred: (*Choose the single best lettered response from the following choices.*)
a. After World War II.
b. In 1,382 CE.
c. In 1,382 BCE.
d. Over 4,000 years ago.
e. Over 12,000 years ago.

2. In Traditional Chinese Medicine, a **meridian** is: (*Choose the single best lettered response from the following choices.*)
a. A specific internal organ related to a specific area of skin or of the body.
b. A specific area of skin or of the body related to a specific internal organ.
c. A retroauricular area of skin.
d. Part of the perineum.
e. Part of the oral cavity.

3. Worldwide, psoriasis affects up to: (*Choose the single best lettered response from the following choices.*)
a. 0.3 percent of the population.
b. 3 percent of the population.
c. 8 percent of the population.
d. 11 percent of the population.
e. 15 percent of the population.

4. In Traditional Chinese Medicine, the terms "yin" versus "yang," applied to food, refer to: (*Choose the single best lettered response from the following choices.*)
a. Bitterness versus sweetness.
b. Coldness (low temperature) versus warmness (high temperature).
c. Coolness (calming) versus hotness (stimulating).
d. Dryness versus wetness.
e. Texture.

5. Studies on the effectiveness of Traditional Chinese Medicine have produced mixed results to date. Which of the following have been found not to be more effective than Western medicine in at least one study? (*Choose as many as apply. All, some or none of the following lettered responses may be correct.*)
a. Keingai-rengyo-to against *Propionibacterium acnes*.
b. Weng-tong-hua-yu against moderate to severe plaque psoriasis.
c. Zemophyte against atopic dermatitis.

ANSWERS TO EXAMINATION:

1. d 2. b 3. b 4. c 5. a,b,c.

Formulary of Dr George C. Andrews

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Aq. dest q. s. ad	3 xxxii

Submitted by Douglas D. Altchek, MD, New York, NY

From the Departments of Pathology and Dermatology, Rutgers University – New Jersey Medical School, Newark, NJ

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CORE CURRICULUM

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Alopecia Areata—Part I: Background

Juliany Estefan, MD;[1] Marcia Ribeiro, MD, PhD;[2] Eliane Abad, MD;[3] Simone Saintive, MD;[3] Marcia Ramos-e-Silva, MD, PhD[4]

Alopecia areata is a trichosis characterized by loss of hair, with the abrupt onset of round or oval, nonscarring, flat, single or multiple areas of alopecia lesions, which can coalesce. Several hypotheses have been raised to explain its etiology, with autoimmunity being accepted until today, along with genetic factors. (*SKINmed.* 2015;13:42–53)

Alopecia areata (AA) is characterized by the abrupt onset of single (most common) or multiple round or oval-shaped, nonscarring, flat areas with hair loss, which can coalesce, with normal skin coloration.[1] Less common presentations can be observed in a minority of patients, including reticular AA, ophiatic AA, ophiatic inversus AA (sisapho), diffuse acute AA, and total AA.[2]

AA affects the scalp in 90% of cases[3,4] but can occur in any hairy area (such as the eyebrows, eyelashes, beard, and pubic hair),[2,5] Its course is unpredictable and may evolve with recurrences. More than half of cases resolve in the first year of the disease, irrespective of treatment.[6]

HISTORY

Alopecia was clinically described for the first time by Celsius (37–14 BCE),[2,7] but the designation alopecia areata was given by François Sauvages (1706–1767) in France in 1760.[2,8] *Alopecia* means "loss of hair" and *areata*, from Greek, means "temporary," according to Skinner,[9] although *Dorland's Dictionary*[10] refers to areata as occuring in patches and *Stedman's Dictionary* as occurring in circumscribed areas.[11]

Several hypotheses have been raised to explain the causes of AA. In 1843, David Gruby (1810–1898) suggested a fungal etiology; however, the hypothesis was dismissed by Ferdinand von Hebra (1816–1880). Friedrich von Bärensprung (1822–1864) proposed the trophoneural theory, while Lucien Jacquet (1860–1914) the dystrophic theory, which considered infectious spots as the cause of AA; however, all were discharged.[2] In the 1950s, Stephen Rothman (1894–1963) and Eugene Van Scott (1921–) considered the autoimmune disease hypothesis,[12] an assumption that is accepted today, along with the disease's genetic substrate.[3]

EPIDEMIOLOGY

AA affects approximately 0.1% to 0.2% of the population,[13] with both sexes being equally affected.[14] A few studies, however, show a significant predominance in adult men.[15,16] The incidence peaks between the ages of 20 and 50 years, but the disease may be diagnosed at any age.[2] Approximately 20% of AA cases occur in the pediatric population,[17] and up to 60% of patients present with their first alopecia before age 20.[18] A poor prognosis is associated with onset at an early age.[19] AA may occur as a single, self-limited episode, but may also evolve with various simultaneous or recurring lesions with intervals from a few months to many years.[20]

ANATOMY AND CYCLE OF THE PILOSEBACOUS FOLLICLE

Anatomy of the pilosebacous follicle

Humans have about 5 million hair follicles all over the body,[21] except for the palms, lips, glans and penis, nail beds, and lateral

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side of the fingers.[22] The scalp has approximately 100,000 hair follicles.[21] This is the structure where the hair originates, and its development begins between the 8th and 12th week of gestation.[22,23] After birth, there is no formation of new follicles, but there is a tendency to the reduction of hair follicle density from 1.135/cm^2 at birth to 616/cm^2 into adulthood.[22]

The sebaceous gland, pilar erector muscle, and hair follicle jointly form the pilosebaceous unit. This is a complex structure that has a large number of epithelial and mesenchymal cells. The hair follicle is divided into two segments. The superior area is stable and not affected by the hair follicle cycle, while the bottom is active during hair cycle stages, almost completely regressing during catagen and telogen stages. The insertion of the erector muscle is the limit between the superior and inferior follicle. The upper part comprises the ostium (skin follicle opening), infundibulum (segment extending from ostium to point of sebaceous gland insertion), and isthmus (between the opening of the sebaceous gland and the insertion point of the hair erector muscle).[23] The lower part extends from the insertion of the hair erector muscle up to the hair bulb. Matrix cells and melanocytes surrounding the dermal papilla are present in the bulb. This is the region of the greatest mitotic and metabolic activity.[24]

Two hair follicle anatomical divisions have been established: the longitudinal and the transversal.[21] In the latter, the acellular vitreous membrane, outer root sheath, inner root sheath (Henle layer, Huxley layer, and cuticle inner root sheath) and hair stem, formed by the cuticle, cortex, and medulla, have been shown.[25]

Hair color is determined by melanocytes, which are more pigmented during the growth phase as a result of follicular melanocyte activity.[26] It is likely that in other stages, melanocytes decrease in size, and some enter into apoptosis.[21] Follicular melanocytes present some differences when compared with epidermal melanocytes; the former are larger and have longer dendrites. In addition, they are associated with four or five keratinocytes, while the epidermal melanocytes are associated with 36 to 40 keratinocytes.[27]

Hair is classified into three types based on texture and size: lanugo, vellus (or intermediate), and terminal. Lanugo hair has no marrow,[22] is thin, slightly pigmented, and soft, which develops in the fetus after the 20th week[21] and disappears after birth.[22] It can sometimes be observed in adults with various forms of hypertrichosis and in hypertrichosis lanuginosa hereditary syndrome.[22]

Vellus hair replaces the lanugo after birth. It is short hair that is less than 1 cm in length and between 0.03 mm and 0.06 mm in diameter.[21] It may constitute up to 7% to 25% of hair in terminal areas such as the scalp.[28]

Intermediary hair is observed for the first time after delivery, following the initial lanugo. It is characterized by a rough cuticle and scarce and fragmented pigmentation.[28]

Terminal hair is the most pigmented and has a diameter of more than 0.06 mm and a length of more than 1 cm.[21] It is found on the scalp, underarms, pubic regions, eyebrows, eyelashes, and beard. The size and shape of terminal hair vary according to location and function. On the scalp, for example, it works as protection against UV radiation and as a thermal insulator.[28]

Cycle of the pilosebaceous folicle

Growth of each hair follicle usually occurs in cycles.[26] The cycle of the pilosebaceous folicle is coordinated by hormones, cytokines, transcription factors, and their corresponding receptors and is carefully regulated by the endocrine, paracrine, and autocrine system. Disruption of these cycles can entail the development of alterations in the hair.[26,28] It is possible for an individual to have 10 to 20 cycles of hair growth during a lifetime.[21] The rate of hair growth is approximately 2.5 mm per week,[22] and normal daily hair loss is around 50 to 150 hairs.[21]

There are three main hair growth phases: anagen, catagen, and telogen phases. The anagen stage is the longer-lasting stage, lasting approximately three years, and is divided into six stages. The first five are called pro-anagen and the sixth is called metanagen.[26] The anagen phase is haracterized by complete follicle development in active growth. About 75% to 100% of normal scalp follicles are in this stage.[29]

Catagen is the resting phase, a transitional stage between the anagen and telogen stages.[26] Less than 1% of hair is found in this stage,[21] and it lasts approximately 4 weeks.[26]

The hair loss stage is called telogen and lasts 3 to 4 months, representing almost 10% of hair follicles.[26] Some research has suggested that there are two other phases: the exogenous phase, which is a specific and highly controlled hair follicle process where it has been shown that the exclusion of the hair rod is an active process that differs from the quiescent telogen stage;[30] and the kenogen stage, which represents the empty follicle after the telogen phase and before a new anagen phase. This is a new phenomenon in hair cycles. This stage is observed in healthy skin; however, the frequency and duration tends to be greater in men and women with androgenic alopecia (AA).[31]

By the end of the anagen stage, the hair bulb comes closer to the surface, through the remodeling of the follicle portion below the bulge. The concentric layers of the inner root sheath, which anchors the hair to the follicle, are present only on the bottom

of the follicle's isthmus. Consequently, the telogen hair does not firmly adhere to the tissue, as occurs in the anagen phase, and may come off easily upon gentle traction. The beginning of the growth of new anagen hair leads to loss of any residual telogen hair in the follicle channel.[26]

As age advances, anagen stages get shorter, and the interval between the two phases increases.[32]

In AA, this cycle is altered. In the anagen phase, the follicle can become inflamed and is kept in a dystrophic anagen state, unable to produce normal hair.[33]

ETIOPATHOGENESIS

AA is a chronic disease of the hair follicles, likely multifactorial, with genetic and autoimmune components.[2,34] Pathogenesis of AA and the molecular mechanisms that lead to hair loss are still poorly understood. In the past, it was believed to be an infectious process of neutrophilic origin.[35]

One study detected a cytomegalovirus DNA in the scalp lesions, but these findings were not confirmed in subsequent studies by polymerase chain reaction analysis of peripheral blood.[36] A study that attempted to associate AA with *Helicobacter pylori* showed inconclusive results.[37]

AA is also a common clinical finding in patients with vitamin D deficiency, vitamin D–resistant rickets, and mutation of the vitamin D receptor.[38] The relationship between vitamin D levels and the development of AA and whether vitamin D supplementation can help in AA treatment is undergoing research.[39]

It was recently shown that AA is an inflammatory disease likely to be an autoimmune disorder.[40] This hypothesis is supported by the association of AA with autoimmune diseases in the presence of lymphocytic infiltrates around affected hair follicles and in the clinical improvement seen with immunosuppressive drug use.[12]

GENETIC FACTORS

A positive family history is present in 10% to 25% of patients with AA,[41,42] with this positivity increasing in individuals with early onset of the condition.[2] Some factors strengthen the association of AA with genetic factors, including the higher incidence in individuals with Down syndrome, human leukocyte antigen (HLA) associations, and atopy, which is a hereditary condition,[2] and the occurrence of AA in twins, with 55% concordance in monozygotic twins.[43] The presence of atopy is twice as common in patients with AA than in the general population.[44]

The AA phenotype can vary from slight loss of hair to involvement of all body hair, making it a multifactorial disease with complex characteristics.[45] The suggested inheritance is autosomal dominant, with variable penetrance.[46]

In 2007, a study seeking to define the genetic basis of AA with 20 families (102 individuals with AA and 118 individuals without AA in the United States and Israel) was performed. Analysis showed at least four susceptibility locations in chromosomes 6, 10, 16, and 18.[47] HLA is associated with susceptibility to AA, which is coded by the major histocompatibility complex and is located in chromosome 6—these are likely the main susceptibility locations in this disease.[45]

Several genetic studies on AA have focused on HLA antigens because of the disease's immunological aspects48 and some have shown an association between alleles and AA, such as HLADQB1*03,[49,50] HLA-DRB1*04,[51] HLA-RB1*11, HLADRB1*07, HLA-DRB1*08,[52] HLA-DR4, HLA-DR5, HLA-DR11, and HLA-DQ7.[48] Moreover, there are alleles that have shown protective factors for AA, such as HLA-DR52, HLA-DQB1*06, HLADRB1*13, and HLA-DRB1*03.[52,53]

The MX1 gene encodes protein induction of INFp78 (MxA), which gives resistance to the influenza virus and is expressed in lesions of anagen hair bulbs of patients with AA, but not in normal follicles. Researchers conducted a case-control study to evaluate MX1 polymorphism in 165 patients with AA and 510 controls and found a significant association between the marker and AA (odds ratio, 1.79; P=.0036), in addition to an increased risk for the plaque form and onset at an early age (odds ratio, 2.34; P=.0072). With these results, the MX1 gene was suggested as possibly a new candidate gene for AA.[48]

IMMUNOLOGICAL FACTORS

The immune system consists of a network of organs, cells, and molecules that aims to maintain body homeostasis by combating various aggressions.[54]

Immunity is divided into (1) innate, or natural or native, and (2) adaptive or acquired. The former corresponds to the initial response, which is faster and responds to a large number of stimuli, but it is limited and unspecific, because it does not develop immunologic memory. It does not depend on previous contact with aggressive agents and can stimulate the acquired response to improve defense against infections. The main components of this response are physical and chemical barriers (epithelium and antibacterial substances on epithelial surfaces), phagocytic cells, blood proteins, and cytokines. Primary effector cells of innate

immunity are macrophages, neutrophils, dendritic cells, and natural killer (NK) cells.[54,55]

The adaptive immune response is a late phenomenon that depends on an elaborate reactivity in various stages of activation of specialized cells, such as lymphocytes and molecules produced by them. It is a highly specific response that triggers immune memory. Cells involved in this response are lymphocytes and cells that present antigens (APCs). APCs present antigens associated with molecules of the main histocompatibility complex to T lymphocytes, activating them.[54,56] The magnitude and defense capability of this response increases with subsequent exposure to a particular microorganism.[55]

Cytokines are polypeptides that regulate immunological reaction; their action can be local or systemic. A particular cytokine often stimulates the synthesis and action of others.[55]

Tumor necrosis factor (TNF) is the primary mediator of acute inflammatory response to Gram-negative bacteria and other microorganisms. Its name stems from its original identification as a substance present in serum that causes tumor necrosis. Its function is to recruit and activate neutrophils and monocytes to areas of infection, trying to eradicate etiologic agents. TNF is also called TNF-α to differentiate it from TNF-β (also known as lymphotoxin).[55]

Along with TNF, interleukin (IL) 1 plays a role in natural immunity. Its main function is to mediate inflammatory response of the host to infectious pictures or other stimuli.[55] TNF-α and IL-1 activate fibroblasts, promote adhesion and chemotaxis of leukocytes, and trigger systemic changes, such as fever, loss of appetite, and increased heartbeat rate.[54] The main source of these cytokines are macrophages.[54] There are two forms of IL-1: IL-1α and IL-1β. They link to the same receptors and have the same biological activities.[55]

The interferon family mediates natural immune response to virus infections. It inhibits viral replication and increases expression of MHC class I molecules.[55]

IL-2 functions as a growth factor, acting primarily in cells that produce it or in adjacent cells. It is mainly produced by CD4+ T lymphocytes. It is important for survival and function of regulatory T cells, which are a subset of CD4+ T cells. These suppress immune responses and maintain autotolerance. The latter is important, because tolerance to antigens is vital for normal immune system function, and changes in self-tolerance can lead to autoimmune diseases development.[55]

IL-4 is the most important cytokine from the Th2 subgroup. It acts as an inductive and effector of these cells. It is the main stimulus for production of IgE antibodies and is also active in reactions mediated by mast cells and eosinophils. Their main sources are CD4+ T lymphocytes from the Th2 subset and activated mast cells.[55]

Interferon gamma (IFN-γ) is the main macrophage activating cytokine. It has a role in natural and acquired immunity against intracellular microbes.[55] It has an antiviral, immunoregulatory, and antitumor role, in addition to an important activity in chronic inflammation.[54] It stimulates class I and II MHC molecule expression[55] and its main source are T and NK cells.[54]

IFN-γ has a role in AA as the main altered cytokine, mediated by CD4+ Th1 response.[57] Some studies showed higher IFN-γ serum levels in total or universal AA. There was no significant difference in levels of IFN-γ in patients with localized AA.[57,58] Thus, it was suggested that the dosage of IFN-γ in serum could be a useful prognostic indicator that may help identify patients likely to develop alopecia universalis.[58]

IL-2 and IFN-γ levels are increased in patients with extensive disease, as are IL-1α and IL-4 serum levels significantly increased in patients with localized AA.[59]

Normal anagen hair follicles are immunologically privileged, working as a defense to an autoimmune "attack."[60] Due to the influence of certain factors (infections, trauma, or physical or psychologic stress), there is autoantigen exposure and subsequent triggering of autoimmune responses. The proximal area of epithelial anagen hair follicles root sheath produces IFN-γ, which activates CD8+ T cells that can react against autoantigens via MHC class I. Cytokine release activates a secondary response involving CD4+ T cells, Langerhans cells, and macrophages, increasing follicular damage and leading to AA.[61] Therefore, immunomodulatory therapies (steroids, contact immunotherapy, cyclosporine A, and psoralen + UVA) are viable treatment options for AA.[39]

IL-1 is a powerful inductor of hair loss.[57] Like IL-1, TNF-α also inhibits hair follicle growth. In vitro, it produces some follicular morphologic alterations similar to those observed in AA.[62]

Researchers[52] investigated IL-4 and total IgE serum levels in patients with AA without atopy. They observed that 48.3% of patients with AA had high IgE and IL-4 levels, especially in cases of universal AA and chronic disease.

There is a higher incidence of autoimmune diseases in patients with AA than in the general population, including atopy,[44] thyroid autoimmunity,[63] vitiligo,[44] psoriasis, systemic lupus erythematosus, and polyglandular autoimmune syndrome.[64]

In autoimmune disorders, autoantibodies and circulating proteins produced by B lymphocytes are found and have a role in disease pathogenesis.[55] Presence of autoantibodies that react against keratinocytes and melanocytes in AA are mentioned in the literature. The presence of these melanocytic antibodies could explain the initial regrowth of white hair and the association with vitiligo.[65] The overall incidence of this association is 3% to 8%, with 1% in the US population.[44]

Studies have detected antibodies against hair follicle structures in the anagen stage by immunofluorescence in approximately 90% of patients with AA, compared with 37% in controls.[66] The presence of specific autoantibodies from other diseases in AA has also been reported.[67]

High levels of antinuclear factor (ANF), which is associated with autoimmune rheumatologic diseases such as systemic lupus erythematosus and rheumatoid arthritis, is found in the serum of patients with AA.[68] Thyroid antimicrossomal antibodies, antiparietal gastric antibodies,[69] and antibodies against smooth muscle[70] have also been detected.

Thyroid autoimmunity is primarily associated with AA, with an incidence ranging from 8% to 28%[63]; however, the presence of thyroid autoantibodies has no clinical correlation with AA's severity.[71] Routine screening for autoimmune diseases, particularly thyroid disease, is not indicated because of lack of clinical evidence.[72]

The association of AA with some genetic diseases, such as Down syndrome, is reported in the literature.[64] There may be an increased risk of type 1 diabetes in relatives of patients with AA; in contrast, patients themselves may have a reduced incidence compared with the general population.[73]

Autoimmune polyendocrinopathy associated with candidiasis and ectodermal dystrophy is an autosomal recessive syndrome that evolves with mucocutaneous candidiasis, hypoparathyroidism, and Addison disease.[74] This syndrome is associated with several autoimmune diseases, including AA. Its genetic basis is a mutation in the gene that encodes the autoimmune regulator (AIRE) mapped at 21q22. 3.[74] AA risk in patients with this condition is 30% and is associated with severe disease and early onset[75]; however, AIRE mutations are not associated with AA in the general population.[76]

ENVIRONMENTAL FACTORS

The discrepancy of AA in twins suggests that it is triggered by environmental factors in susceptible hosts.[77] Some environmental factors have been thought to be related to the etiology of AA, such as infections, emotional stress, diet, and some toxins, although this is not confirmed.[37]

CLINICAL PRESENTATION

Lesions are typically asymptomatic, but itching or burning may be present and mild erythema and edema may occur during the development of the lesions.[2] At the beginning of hair regrowth, white hair may emerge[2,13]; however, pigmentation tends to return over time.[78]

Peladic plaque hair forms an exclamation mark shape and can be observed in the lesion's periphery. These are thinner and less pigmented hairs at the emerging point, with greater thickness at the distal end. Peladic plaque hairs demonstrate the Widy sign, which corresponds to melanin pigment deposition in the shaft but is not pathognomonic.[2]

Familiar AA behaves as a conventional type clinically. It constitutes 10% to 20% of AA cases, and transmission appears to be autosomal dominant with incomplete penetrance.[42]

The disease's course is variable. There may be spontaneous hair regrowth after a few months, especially in more benign forms of single small lesions, or appearance of new plaques after 3 to 6 weeks.[79] The surface areas of AA may show mild atrophy without cicatricial alopecia patterns and follicular hyperkeratosis.[2,5]

The clinical picture is variable and the patient can present with localized small and well-localized lesions or involvement of all body hairs.[3]

Single or unifocal patch and multifocal multiple patches of AA

Unifocal AA presents clinically as a single rounded or oval alopecia plaque, with a flat skin surface and normal skin staining (Figures 1–8). The single lesion is the most common form, while the multifocal form is characterized by multiple typical AA plaques.[2,3]

AA totalis and AA universalis

Total AA corresponds to the loss of all hair of the scalp (Figure 9), without alteration of body hair, while AA universalis involves the loss of all body hair. Approximately 5% of cases will evolve to totalis or universalis alopecia.[80]

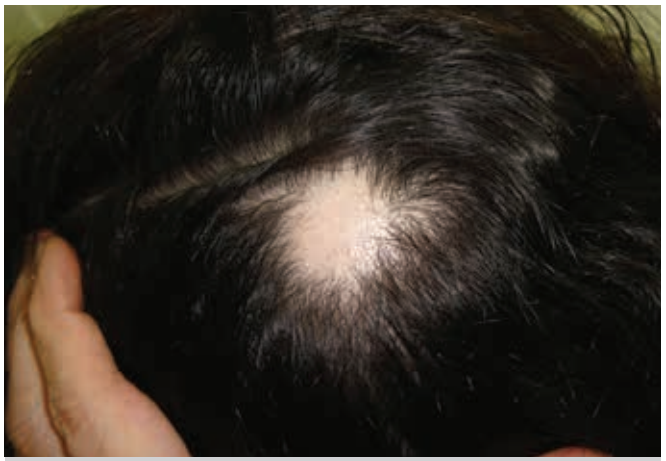

Figure 1. Single round plaque of alopecia areata of the scalp.

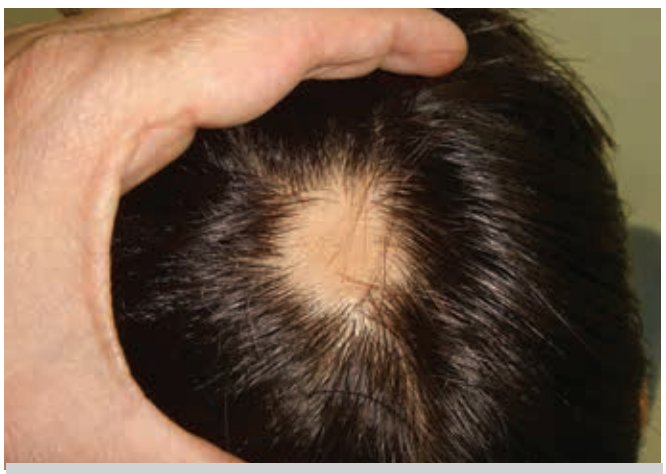

Figure 2. Single round patch of alopecia areata of the scalp.

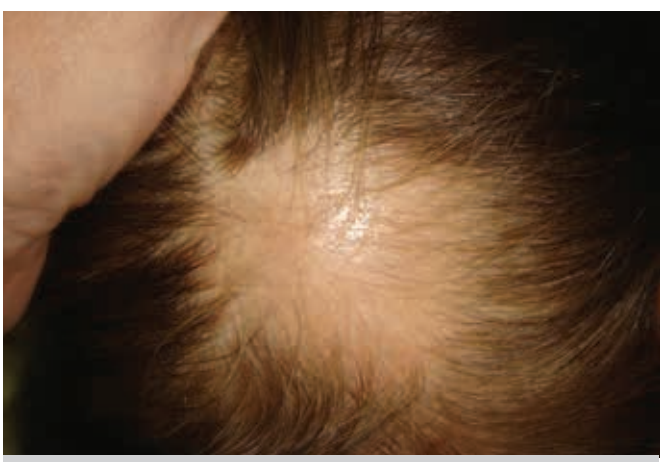

Figure 3. Single oval patch of alopecia areata of the scalp.

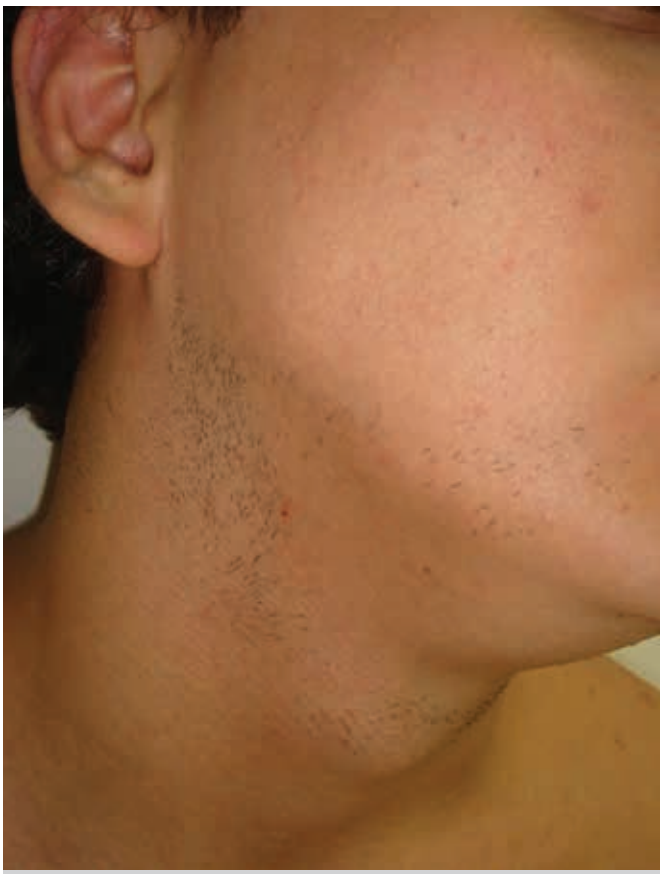

Figure 4. Alopecia areata of the beard.

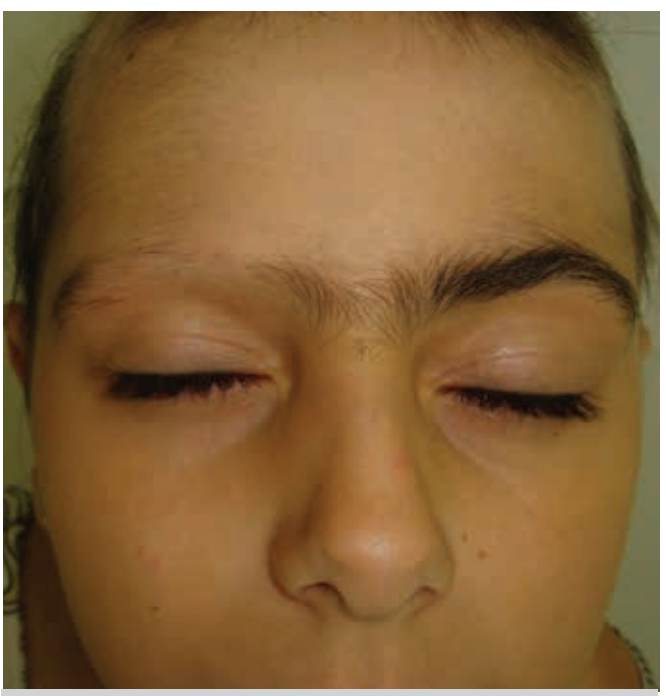

Figure 5. Alopecia areata of the eyebrow.

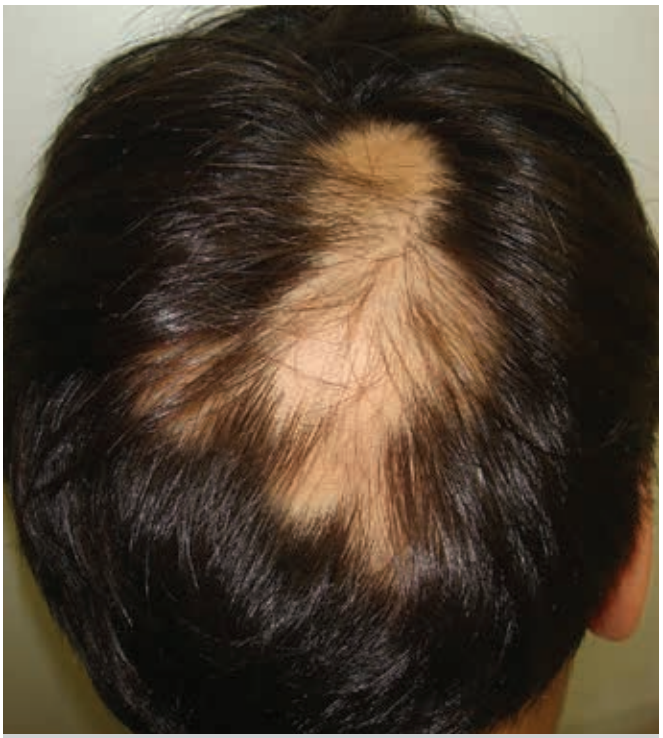

Figure 6. Multiple coalescent patches of alopecia areata on the scalp.

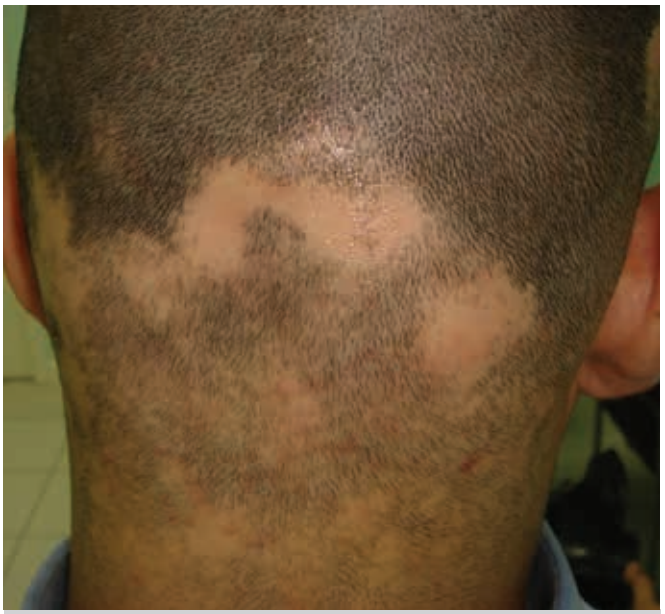

Figure 8. Multiple patches of alopecia areata on the occipital region.

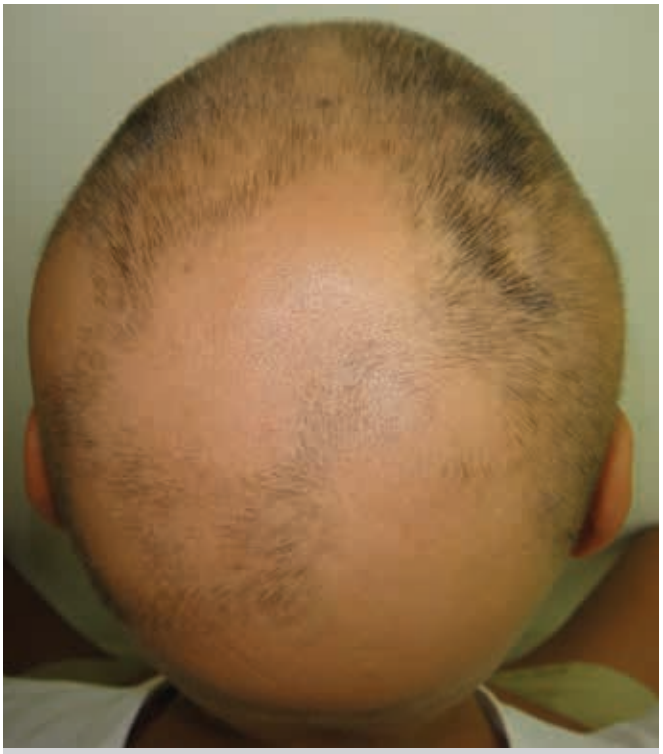

Figure 7. Multiple patches of alopecia areata on the scalp.

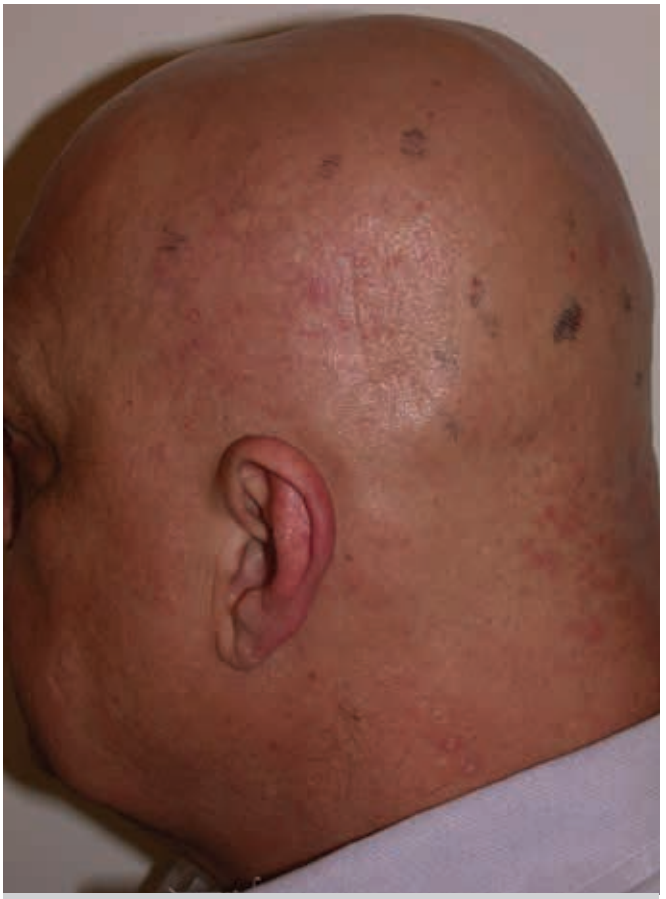

Figure 9. Total alopecia areata.

Ophiasic AA and inverted ophiasic alopecia areata

Ophiasic AA is clinically presented by loss of hair in the temporo-occipital region (Figure 10), and reverse ophiasic AA or Sisaifo corresponds to loss of all scalp hair except for that on the lower margins, along the line of temporo-parietal implantation, displaying its reverse ophiasic denomination.[2]

AA reticularis

AA reticularis evolves with multiple AA plaques separated by preserved bands of hair that forms a reticulated aspect.[2]

Diffuse AA

First described by Kawamura-Sato and colleagues[81] in 2002, and most recently reported by Lew and colleagues[82] in 2009, this new variant is characterized by rapid, diffuse, and acute progression, with extensive involvement.[3] It features areas of thinning hair, which may be an early form (especially in children and adolescents), or may arise from the plaque forms. Most patients with diffuse AA evolve to alopecia totalis or universalis. This form is difficult to diagnose and should be differentiated from acute telogen effluvium, androgenetic alopecia, and patchy alopecia of syphilis.[2]

AA incognito

AA incognito is a rare form, most commonly seen in women (86.6%) between the ages of 20 and 40 years. It is characterized by sudden and intense diffuse loss of hair. It differs from telogen effluvium and androgenetic alopecia because it presents with typical clinical, dermoscopic, and histopathologic features of classic A and its prognosis is good. Positive traction test and trichodynia can be observed. There is no hair thinning, unless hair loss persists for months or years.[83–86]

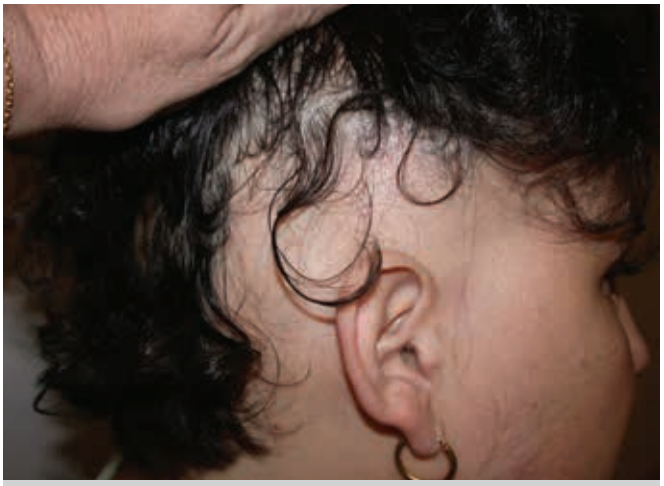

Figure 10. Ophiasic alopecia areata.

Congenital AA

Congenital AA has been classified as an acquired disease; however, Lenane and colleagues[19] reported four cases of congenital AA. Diagnosis was clinical and the patients were followed for 3 to 5 years, with several treatments, achieving re-pilation with 0.05% clobetasol propionate in 50% of treated patients. This form's differential diagnoses are rickets, scalp hereditary hypotrichosis, Marie Unna hypotrichosis, atrichia, triangular alopecia, tinea capitis, and neonatal telogen effluvium.

Perinevoid AA

Perinevoid AA corresponds to the loss of hair around a melanocytic nevus.[87]

EXTRAFOLLICULAR INVOLVEMENT

Ungual alterations

Nail involvement can be seen in AA, with a frequency of 7% to 66%.[88] Some authors report greater frequency in children (12%) than in adults (3.3%).[89] These may occur before, during, or after AA lesions.[2]

Nail disorders, especially in children, may precede the onset of AA by years.[90]

The prevalence of nail involvement is higher in more severe forms, with 15.4% in AA universalis, 3.7% in AA totalis, and 2.25% in plaque AA.[91]

Nail changes, including geometric pitting, striated lunulae, and trachyonychia, expressing an inflammation process of the nail matrix, can be observed. Nonspecific signs may also be evidenced, including leukonychia punctata, Beau's lines, and onychomadesis.90 There is no consensus between nail lesion severity and disease prognosis. Some authors report that the degree of involvement is not related to the prognosis of AA,[90] while other studies have suggested that the nail changes are associated with a greater extent of hair loss.[88]

No treatment is necessary as the changes spontaneously normalize.[90]

Geometric pitting:

Geometric pitting consists of shallow, small, cupuliform depressions, with regular distribution, forming geometrical shapes (Figures 11 and 12).[90] It is the most frequent form of nail alteration observed in AA.[88]

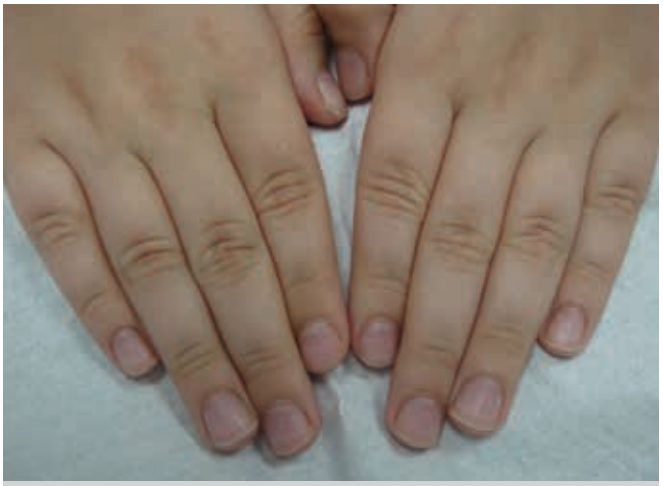

Figure 11. Ophiasic alopecia areata.

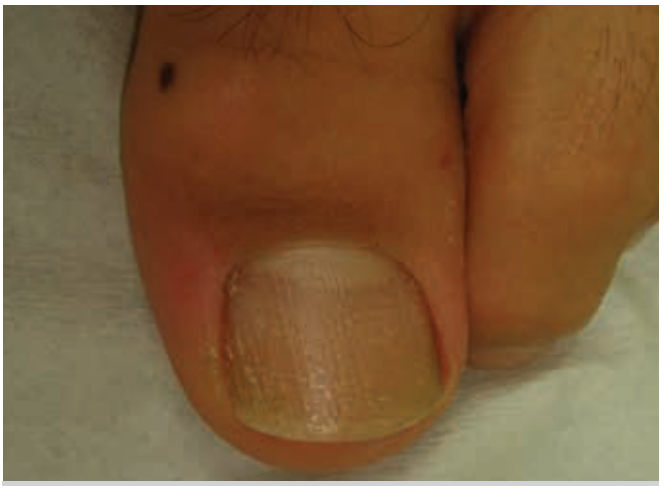

Figure 12. Ophiasic alopecia areata.

Striated lunulae:

Striated lunulae are irregularly shaped erythematous patches. They are generally associated with pitting and trachyonychia.[87,90]

Trachyonychia:

In trachyonychia, nail plates present a wrinkled appearance with fine longitudinal striae (Figure 13). It may not affect all nails.[90,92]

Leukonychia punctata or transversal:

Leukonychia punctata or transversal is typical in childhood and is usually caused by microtrauma. It is characterized by the appearance of small white spots that disappear before reaching the distal margin of the nail.[88,90]

Beau's lines:

Beau's lines present as transversal ridges, sharper in the center of the nail plate. They tend to progress distally as the nails grow. They represent temporary interruption of the proximal matrix mitotic activity. They can be triggered by microtrauma (eg, manicure or onychotilomania), dermatologic diseases (eg, contact dermatitis, erythroderma, or paronychia), or systemic diseases (eg, antiblastic chemotherapy, dysmenorrhea, fever, or peripheral ischemia).[90,92]

Onychomadesis:

Onychomadesis occurs when the nail plate detaches from the proximal nail fold. It is caused by temporary interruption of mitotic activity of the nail matrix. Its causes are similar to those of Beau's lines, but the intensity of the damage to the matrix is more severe.[90,92]

Figure 13. Trachyonychia.

Koilonychia:

Koilonychia presents with central depression of the nail plate with lifted edges, causing a concave aspect (spoon shape). The nail is usually thin and fragile. It has several causes, other than AA, such as iron deficiency, psoriasis, lichen planus, and thyroid diseases or can be physiological in childhood.[92]

Onycholysis:

Onycholysis corresponds to the separation of the distal plate from the nail bed.[90]

Onychorrhexis:

Onychorrhexis is characterized by fissures and longitudinal grooves on the nail plate.[92]

Ophtalmological alterations

Several ocular changes associated with AA have been described, including lens opacities (51%), fundoscopic changes (41%),[93] papillar ectopy,[94] posterior subcapsular cataract,[95] Horner syndrome,[94] retineal focal hypopigmentation,[96] miosis,[97] iris atrophy,[94] palpebral ptosis,[97] heterochromia,[94] and decreased visual acuity.[95]

Salmon patch on the nape

In one investigation, a total of 199 AA patients and 215 controls without AA were examined for salmon patch on the nape. A total of 17.6% of patients in the AA group had the patch compared with 9.3% in the control group (odds ratio, 2.08; 95% confidence interval, 1.43–2.73; P=.013). A statistically significant association between the presence of the salmon patch and the duration of AA was reported (P<.001) and the presence of the patch was associated with the severity of AA (P<.001).[98]

Another study conducted in 2005[99] also investigated this association and suggested a relationship between salmon patch and AA particularly in more severe and chronic forms.

Psychiatric diseases

Increased risk of psychiatric disorders in patients with AA, especially anxiety and mood disorders, has been described in the literature.[100] It is known that these diseases can act as triggers for the onset of the clinical picture, but may also be secondary to the cutaneous picture.[2,101]

CONCLUSION

AA is a benign condition, with probable autoimmune etiology and genetic predisposition. The clinical picture may be unstable, with periods of improvement and deterioration, which can trigger psychologic repercussions. The hair follicle is not destroyed in AA; therefore, there is potential for localized hair regrowth.

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NEW THERAPY UPDATE

William Abramovits, MD; Aditya K. Gupta, MD, PhD, FRCPC, Section Editors

Tavaborole 5% Solution for Onychomycosis

Aditya K. Gupta, MD, PhD, FRCPC;[1,2] Deanne Daigle, MSc;[2] William Abramovits, MD[3,4,5]

Onychomycosis is a stubborn fungal infection of the nail plate and nail bed.[1] If left untreated, it can spread to adjacent nails, to additional body sites, or to other individuals.[2] Oral terbinafine is the gold standard of treatment,[3] and its efficacy can be attributed to systemic dispersion to the nail bed.[4] For a number of patients, however, the risks associated with the use of oral antifungals to treat onychomycosis outweigh their potential benefit.[5] Patients who are taking multiple concomitant medications or who have compromised immune function may have a greater risk for complications associated with the use of oral antifungals, while some patients simply do not wish to initiate systemic therapy for a seemingly innocuous "cosmetic" problem.[6–8] Topical therapy is often a feasible avenue for these patients; however, successful treatment is constrained by these agents' limited ability to penetrate the nail.[9]

In some cases, systemic and topical treatment options can be exhausted. Patients with difficult to treat onychomycosis may have failed systemic therapy, topical treatment with ciclopirox lacquer, or a combination of both. Onychomycosis in these patients may be caused by resistant strains of fungi that do not respond to conventional therapies.[10] For more than a decade, there were no alternatives to ciclopirox nail lacquer, as it was the only topical agent approved for this indication in North America.[11] Tavaborole 5% solution is one of two novel topical antifungals for the treatment of toenail onychomycosis. Tavaborole has an enhanced ability to penetrate the nail plate and a unique mechanism of action against pathogenic fungi.[12–14] Tavaborole 5% solution received approval from the Food and Drug Administration in July 2014.[15]

PHARMACOLOGIC PROFILE

Tavaborole (formerly AN2690), is a member of the novel drug class of boron-containing compounds called oxaboroles. Oxaboroles were derived from a previous class of antibacterial borinic acid quinolone ester compounds, specifically selected for their antifungal properties.[16] Unlike existing antifungals that inhibit ergosterol synthesis (terbinafine, itraconazole, fluconazole, amorolfine, efinaconazole), or microbial metabolism (ciclopirox),[17] tavaborole interferes with the protein synthesis in fungal cells[18] by acting on aminoacyl-transfer RNA (tRNA) synthetases. Tavaborole specifically binds with these enzymes in the editing site, thus preventing the synthesis of leucine-charged tRNAs and ultimately suppressing fungal cell activity.[18]

In vitro nail penetration studies show that tavaborole is better able to penetrate human nails compared with ciclopirox 8% and amorolfine 5% nail lacquers.[13,14] Tavaborole also retains its antifungal effects in the presence of keratin. The minimum inhibitory concentrations (MICs) of tavaborole range from <0.5 µg/mL to 8 µg/mL, 0.125 µg/mL to 4 µg/mL, and <0.5 µg/mL to 2 µg/mL, for dermatophytes, yeasts, and molds, respectively.[19] Two weeks following the completion of 28 days of treatment with tavaborole 7.5%, nail plate concentrations above these MIC ranges were maintained[20]; furthermore, therapeutic levels of tavaborole remained in the nail up to 3 months after treatment cessation, with drug levels corresponding to 161 times the MIC_{90} for *Trichophyton rubrum*.[20]

EFFICACY IN CLINICAL TRIALS

Several phase II studies have been conducted to investigate the efficacy and safety of various concentrations and dosing regimens of tavaborole for toenail onychomycosis.[21] The phase II portion (NCT 00679600) of a phase I/II open-label study examined the efficacy of tavaborole 7.5% in 15 adults aged 18 to 65 years.[22] Eligible participants had mycologically (potassium hydroxide [KOH]) confirmed onychomycosis of at least one great toenail, a clinical diagnosis of onychomycosis in at least six additional toe-

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Table I. Efficacy Results From Phase II Clinical Trials of Tavaborole (AN2690)

ClinicalTrials.gov Identifier	No.	Primary Outcome Measure	Measurement Moment	Vehicle	AN2690 1%	AN2690 2.5%	AN2690 5%	AN2690 7.5%
NCT00680160	15	Negative culture	2 weeks	–	–	–	–	22/25 nails (88%)
			4 weeks	–	–	–	–	25/25 nails (100%)
NCT00679965	187	Negative culture + ≥2 mm CN or ISGA clear/almost clear	24 weeks	9/63 (14%)	–	9/33 (27%)	8/31 (26%)	19/60 (32%)
NCT00679523 & NCT01278394	89	Negative culture + ≥2 mm CN or ISGA clear/almost clear	24 weeks	–	–	–	13/30 (43%)	16/30 (53%)
			48 weeks	–	–	–	4/29 (14%)	–
NCT00680134	60	Negative culture + ≥2 mm CN or ISGA clear/almost clear	24 weeks	–	9/30 (30%)	–	15/30 (50%)	–

Abbreviations: ISGA, Investigator Static Global Assessment; CN, clear nail.

nails, ≥80% involvement of both great toenails, and a combined great toenail plate thickness of >3 mm. Participants applied tavaborole 7.5% to all 10 toenails and surrounding skin once daily for 28 days. Twenty-five great toenails were evaluated for efficacy by fungal culture or KOH. Results from the phase II studies are summarized in Table I. After only 2 weeks of treatment, toenails treated with tavaborole demonstrated conversion from positive to negative culture.

A double-blind, vehicle-controlled, dose-ranging study (NCT 00679965) was performed to investigate three concentrations of tavaborole compared with vehicle.[21] A total of 187 participants with KOH- and culture-confirmed distal lateral subungual onychomycosis (DLSO) of the great toenail and 20% to 60% involvement of the target nail were enrolled in the study. Participants applied either vehicle (n=63), tavaborole 2.5% (n=33), tavaborole 5% (n=31), or tavaborole 7.5% (n=60) daily for 3 months and then three times per week for the subsequent 3 months. The primary efficacy endpoint was negative culture and either ≥2 mm of clear nail growth or an Investigator Static Global Assessment (ISGA) of clear or almost clear growth at 6 months. All concentrations of tavaborole demonstrated a significantly greater therapeutic effect compared with vehicle after 6 months of treatment (P<.03) (Table I).

Another phase II study was comprised of 89 individuals with KOH- and culture-confirmed DLSO of one great toenail and 20% to 60% involvement of the target nail (NCT00679523 and NCT01278394).[21] Cohort 1 (n=30) was treated with tavaborole 5% daily for 6 months, cohort 2 (n=30) was treated with a 7.5% concentration daily for 6 months, and cohort 3 (n=29) was treated with a 5% concentration daily for 12 months. The primary efficacy endpoint was negative culture and either ≥2 mm of clear nail growth or an ISGA of clear or almost clear growth at 6 months for cohorts 1 and 2, and at 12 months for cohort 3. After 6 months of treatment, efficacy rates were 43% and 53% in cohorts 1 and 2, respectively. Following 12 months of treatment, the efficacy rate was 14% in cohort 3 (Table I). Safety assessments included physical examinations, monitoring of vital signs, and laboratory tests.

A final phase II trial (NCT 00680134) investigated the 1% and 5% concentrations in 60 participants with mycologically confirmed DLSO of the great toenail and 20% to 60% involvement of the target nail.[21] One group (n=30) applied tavaborole 1% daily for 6 months and the other group (n=30) applied tavaborole 5% daily for the first 30 days and then three times per week for the following 5 months. The primary efficacy endpoint was negative culture and either ≥2 mm of clear nail growth or an ISGA of clear or almost clear growth at 6 months. After 6 months of treatment with tavaborole, 30% and 50% efficacy rates were achieved with the 1% and 5% concentrations, respectively (Table I). Adverse events including application site reactions were also documented. Based on the efficacy and safety re-

Table II. Efficacy Results From Phase III Clinical Trials of Tavaborole 5% Solution

ClinicalTrials.gov Identifier	No.	Outcome Measure	Tavaborole 5%	Vehicle	*P* Value
NCT01302119	601	Complete cure	36/396 (9.1%)	3/205 (1.5%)	<.0001
		Clinical cure	109/396 (27.5%)	30/205 (14.6%)	<.001
		Mycological cure	142/396 (35.9%)	25/205 (12.2%)	<.001
NCT01270971	593	Complete cure	26/399 (6.5%)	1/194 (0.5%)	.001
		Clinical cure	104/399 (26.1%)	18/194 (9.3%)	<.0001
		Mycological cure	124/399 (31.1%)	14/194 (7.2%)	<.001

Complete cure: completely clear nail and negative results for both potassium hydroxide (KOH) and culture. Clinical cure: ≤10% visible nail involvement. Mycological cure: negative results for both KOH and culture.

sults from the phase II trials, tavaborole 5% solution was selected for further evaluation in phase III trials.

Two identically designed, randomized, double-blind, vehicle-controlled, multi-center, parallel-group phase III trials were conducted to investigate the efficacy and safety of tavaborole 5% solution applied once daily vs vehicle for the topical treatment of toenail onychomycosis (NCT01302119 and NCT01270971).[23] Eligible participants 18 years and older with DLSO and 20% to 60% involvement of the great toenail were randomized 2:1 to receive either tavaborole 5% (trial 1, n=396; trial 2, n=399) or vehicle (trial 1, n=205; trial 2, n=194) once daily for 48 weeks. Participants were also followed for 4 weeks post-treatment (week 52). The primary efficacy endpoint was complete cure of the target great toenail defined as negative mycology (KOH and culture) and completely clear nail at week 52. Secondary endpoints included clinical cure, defined as an ISGA of completely or almost clear and mycological cure, defined as negative KOH and culture. Rates for the primary and secondary endpoints in the phase III trials are presented in Table II. Overall, once-daily application of tavaborole 5% was significantly more effective than vehicle in the treatment of toenail onychomycosis.

SAFETY

In preclinical safety studies, a concentration of 10 uM of tavaborole did not inhibit the cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.[24] In the phase I portion (NCT00679601) of an open-label phase I/II study, tavaborole 7.5% had very low systemic exposure after 28-day topical administration and no laboratory abnormalities were found.[22] Taken together, data from these studies suggest that there is little risk of drug interactions with tavaborole. The nature, frequency, and severity of adverse events were similar in the phase II and III trials.[21,23] In all studies, none of the serious adverse events were deemed related to tavaborole. In the phase III studies, the frequency of treatment-related adverse events with tavaborole 5% was comparable to vehicle. Application site reactions were the most commonly reported treatment-related adverse events and consisted of application site exfoliation (2.7%), erythema (1.6%), and dermatitis (1.3%), and these were generally mild to moderate and transient.[23]

CONCLUSIONS

Nail permeability and antifungal resistance continue to pose a challenge for the development of new therapies for onychomycosis. Tavaborole 5% solution is the latest in topical treatment for onychomycosis formulated with an enhanced ability to penetrate the dense keratin of the nail plate and offers an alternative option to ciclopirox 8% lacquer. Tavaborole is also part of a novel drug class, the benzoxaboroles, and thus has a unique mechanism of action compared with existing antifungals. Tavaborole 5% solution, either as a monotherapy or in combination with an oral antifungal, may be of benefit to patients who have experienced previously failed therapy with conventional agents. Head to head comparison studies of the efficacy of tavaborole 5% vs. efinaconazole 10% solution in the treatment of onychomicosis would be of interest to the practicing dermatologist.

DISCLOSURES

Aditya K. Gupta is an advisory board member, consultant, investigator, and speaker for Valeant Pharmaceuticals International Inc. He was involved in preclinical studies of tavaborole for Anacor Pharmaceuticals Inc. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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THE HEYMANN FILE

Warren R. Heymann, MD, Section Editor

Infective Endocarditis: Of Heart, Head, and Skin

Warren R. Heymann, MD

Sir William Osler, the veritable icon of modern medicine, first described infective endocarditis (IE) in 1885. The current incidence of IE in the United States is up to 15,000 cases per year, with an in-hospital mortality rate of approximately 20%. Over the past 50 years, risk factors for developing IE have changed from those with pre-existing cardiac valvular abnormalities (ie, congenital defects or rheumatic heart disease) to the use of intracardiac devices and prosthetic valves, in addition to increasing antibiotic resistance. The mean age of diagnosis has increased, especially among the elderly, with an increasing male/female ratio. Staphylococcal and enterococcal IE has increased, while culture-negative cases and those caused by *Streptococcus viridans* have decreased. The cost to society, both economically and in terms of quality of life, remains profound.[1]

CLINICAL FINDINGS

The pathogenesis of IE is occurs in the following sequence: (1) pathogens gain transient access to the bloodstream through routes such as intravenous drug use or iatrogenic procedures, notably dental work; (2) pathogens can rapidly adhere (via platelet fibrin deposition) to mechanically injured valve surfaces (pre-existing valvular disease) or to inflamed valve surfaces (without pre-existing valve disease); (3) some microbes, such as *Staphylococcus aureus*, obtain intracellular access to the valve endothelium, resulting in significant tissue destruction; (4) proliferation of organisms on and in the endothelium leads to formation of valvular vegetations; and (5) subsequent embolization from vegetations into the systemic circulation leads to complications (eg, ischemic stroke, cerebral hemorrhage, meningitis, brain abscess, and mycotic aneurysm).

Pathogen-host interactions are myriad. Infectivity of the organism is influenced by its adherence (which is aided by biofilms) and their ability to produce proinflammatory cytokines and enzymes. The host response will vary based on the integrity of the valvular endothelium, local hemostatic mechanisms, overall immune status of the patient, and gross anatomical abnormalities of the heart (valves and device material). Given the changing demographics of IE, it is believed that key areas of future research should focus on the role of immunosenescence in elderly patients and in understanding the mechanisms that trigger septic shock in these patients, which substantially increases the mortality associated with IE.[2]

IE was previously classified by its mode of presentation (acute, subacute, or chronic). It is now characterized according to the presence of underlying cardiac conditions, location, presence of intracardiac devices, or the mode of acquisition. The diagnosis is based on clinical, microbiologic, and echocardiographic (transthoracic or transesophageal) findings, with the Duke criteria having a sensitivity and specificity greater than 80%.[3] Fever (80%), a new heart murmur (48%), worsening of an existing murmur (20%), hematuria (25%), splenomegaly (11%), splinter hemorrhages (8%), Janeway lesions (5%), Roth spots (5%), and conjunctival hemorrhage (5%) may all be presenting signs. IE may also present with sepsis, meningitis, unexplained heart failure, septic pulmonary emboli, stroke, acute peripheral artery occlusion, and renal failure. Cerebral complications of IE, as previously described, are among the most frequent (up to 20%) and severe.[3]

The dermatologic manifestations of IE, including Osler nodes, Janeway lesions, splinter hemorrhages, petechiae, and clubbing,

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have been recognized since the late 19th century. Silverman and Upshaw reviewed the historical descriptions of the extracardiac manifestations of IE. In 1913, F. Parkes Weber ascertained that Osler recognized their significance, and named the lesions in Osler's honor (despite the fact that these lesions were first described by Etienne Lancereaux in 1873). In 1899, Edward Janeway noted that hemorrhages of the palms and soles were most probably caused by endocarditis.[4]

Classically, Osler nodes appear as red-purple tender, slightly raised cutaneous nodules, often with a pale center. They are most frequently observed on the tips of the fingers or toes, but they may also present on the thenar or hypothenar eminences and sides of the digits. The lesions vary in size from 1 mm to greater than 1 cm, lasting from a few hours to several days.

Janeway lesions are nontender hemorrhagic macules or papules located on the palms or soles, especially the thenar or hypothenar eminences. There is a report of two cases: a 66-year-old woman with a history of rheumatic heart disease and IE caused by *Bartonella henselae* presenting with splinter hemorrhages and Osler nodes; and a 25-year-old man with congenital heart disease and a bicuspid aortic valve who developed IE caused by *Streptococcus oralis* demonstrating tender Janeway lesions. A biopsy of the former demonstrated a neutrophilic pustule with overlying epidermal ulceration and necrosis with extensive fibrinoid necrosis of the vessels associated with neutrophilic infiltration. A biopsy of the latter also demonstrated a leukocytoclastic fibrinoid vasculitis. The authors concluded that there may be both clinical and histologic overlap between Osler nodes and Janeway lesions.[5] Presumably, the pathogenesis of both lesions is caused by microemboli (septic or bland) from cardiac vegetations. While classical, these lesions are not pathognomonic for IE; they may also be the result of bacteremia without endocarditis, such as seen distal to infected intravascular grafts or in cases of systemic lupus erythematosus (in the absence of Libman-Sacks endocarditis). Leukocytoclastic vasculitis of the palms and soles may mimic Janeway lesions.[6]

In a study of the prognostic value of skin manifestations of IE, 497 definite cases of IE (satisfying modified Duke criteria) were evaluated. The investigators were able to assess the dermatologic status of 487 patients. Of these 487 cases, 58 (11.9%) had cutaneous findings, including 39 (8.0%) with purpura, 13 (2.7%) with Osler nodes, 8 (1.6%) with Janeway lesions, and 3 (0.6%) with conjunctival hemorrhages. Five patients (1%) had two skin manifestations. Patients with dermatologic manifestations had statistically significant higher rates of IE-related extracardiac complications than patients without cutaneous signs, especially cerebral emboli (32.8% vs 18.4%), without increased mortality. Also statistically significant were the findings that patients with purpura had larger cardiac vegetations (18.1 mm vs 13.7 mm) and that Janeway lesions were associated with more extracerebral emboli. The authors found that specific skin manifestations of IE are associated with a higher risk of complications and should alert physicians to examine for extracardiac complications, notably with cerebral imaging.

CONCLUSIONS

What are the practical implications of this study? Dermatologists, internists, and infectious disease specialists who care for patients with IE may wish to be even more vigilant for systemic (especially cerebral) complications in patients with IE demonstrating classical dermatologic findings. More importantly, in this era of the changing demographics of IE, it is especially important that dermatologists recognize these manifestations, particularly in elderly patients with implantable cardiac devices. This will enable patients to be adequately assessed by blood cultures and echocardiography to confirm the diagnosis of IE in order to expeditiously institute appropriate therapy.

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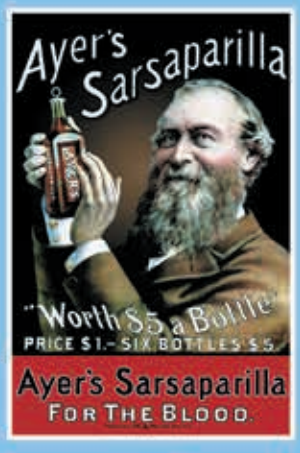

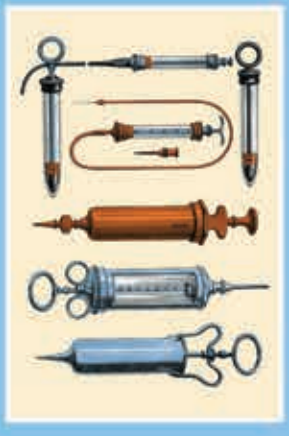

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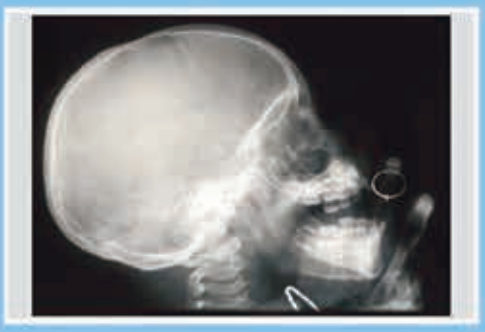

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HISTORY OF DERMATOLOGY SOCIETY NEWSLETTER

Eve Lowenstein, MD, PhD, Section Editor

Hoffman's Drops: The Technique of the Concentrated Neosalvarsan Injection

Mark Bernhardt, MD

"Seyffarth mentions the taste or odor resembling that of Hoffmann's drops ..."
Reviewed by A.W. Stillians. *J Cutan Dis Incl Syphilis*. 1915;33:61.

"Natasha ran indoors, and went on tiptoe to the half-open door of the divan-room, where there was a strong smell of vinegar and Hoffmann's drops."
War and Peace by Leo Tolstoy

Friedrich Hoffmann (1606–1742) was the scion of 2 centuries of physicians. Born in Halle, Germany, he traveled throughout Germany returning home in 1693 to become the first Professor of Medicine at the new University of Halle. Other than two stints in Berlin serving as personal physician to the King of Prussia, Hoffmann remained in Halle until his death in 1742. Hoffmann was considered a gifted clinician as well as a brilliant theoretician. Although highly speculative, his writings served as a bridge from the obsolete humoral model of the past to a modern rational empiricism.

HOFFMAN'S DROPS

Despite all of his wealth and honors, Hoffmann is probably best remembered for a simple concoction of ether and alcohol he described in 1736. He named it liquor anodynus minerali. The rest of the world called it simply Hoffmann's drops. Ether had been discovered in 1275 by the Spanish chemist Raymond Lullius. By combining one part ether with three parts alcohol, Hoffmann created a formulation that was palatable and socially acceptable.

The first devotees of his drops were Europe's titled and elite; King Louis XV of France liked his drops sweetened with sugar. Prominent intellectuals such as Tolstoy, Alexandre Dumas, père, and Søren Kierkegaard were all familiar with Hoffmann's drops. Over time, the popularity of Hoffmann's drops filtered down to the hoi polloi. Women could take Hoffmann's drops without opprobrium in a way they could not drink unalloyed alcohol.

Whatever health claims were made for Hoffmann's concoctions—and it was touted for everything from cough to depression to sea sickness—no doubt its popularity was the result of the combined stupefying effects of its two active ingredients. Although Hoffmann's drops might no longer have the cachet they enjoyed in the 18th century, they have not completely disappeared. You can still buy Hoffmann's drops in Germany where it is sold as an over-the-counter remedy for dizzy spells.

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HISTORICAL VIGNETTE

Charles Steffen, MD, Section Editor

The History of Tuberous Sclerosis Complex: When Skin Gives a Clue

Chiara Giannelli, MD;[1] Emanuele Bartolini, MD[2]

Tuberous sclerosis is a neurocutaneous syndrome characterized by multisystem involvement and an autosomal-dominant pattern of inheritance. It is mainly featured by dermatologic and neurological disorders. The present article reviews tuberous sclerosis history over a period of almost 2 centuries. The pathway towards understanding the association between cutaneous alterations and neurological involvement, which started from the first casual report by Rayer, is described, through the seminal works by Von Recklinghausen, Bourneville, and Pringle, up until the definition of the Vogt triad—epilepsy, idiocy, and adenoma sebaceum. Then, the challenging of these criteria and the widening of the disease spectrum, including patients with normal intelligence, are covered. Eventually the impact of new neuroimaging techniques and advancements in tuberous sclerosis neurobiology are described, with special focus on new therapies and hopes for the future.

Tuberous sclerosis complex (TSC) is an inherited neurocutaneous multisystem disorder characterized by the potential for the presence of hamartomas in almost every organ, most notably in the skin, brain, kidneys, heart, and eyes.[1] The way in which the concept of how the TSC has developed since the 19th century derives from simple clinical observations, pathological studies, and technological advances in diagnostic methods (Table I). The most recent comprehensive review on TSC history dates back to 2008.[2] Our goal was to update the historical literature on TSC, with a novel and special focus on the recent concepts on syndrome genetics and technological advancements.

Table I. Main Steps in Tuberous Sclerosis Complex History

From first reports to syndrome description
1835 Rayer: first case illustration
1862 von Recklinghausen: first syndromic description
1879 Bourneville: Sclérose tubéreuse des circonvolutions cérébrales
1890 Pringle: Pringle's adenoma sebaceum
From neuropathology to early clinical definition
1901 Pellizzi: advancement in neuropathology
1905 Perusini: microscopy of brain pathology
1903 Kothe: recognition of periungual fibromas
1906 Vogt: first diagnostic criteria: Vogt triad
1913 Berg: hereditary nature
1914 Schuster: forme fruste with normal cognition
1918 Lutembacher: first description of lymphangioleiomyomatosis
1920 van der Hoeve: phakoma definition
The new concept of tuberous sclerosis complex
1932 Critchley and Earl: the white spot and psychiatric disorders
1942 Moolten: definition of tuberous sclerosis complex
1967 Lagos and Gómez: 38% of cases have normal intelligence
1979 Gómez: publication of the monograph "Tuberous Sclerosis"
Development of new diagnostic techniques
1987 First applications of brain magnetic resonance imaging in tuberous sclerosis complex
1993 Cloning of TSC2
1997 Cloning of TSC1
2004 Update of diagnostic criteria
2005–2012 mammalian target of the rapamycin signal pathway and experimental drugs

OBSERVING THE SKIN: HOW IT ALL BEGAN

The history of the tuberous sclerosis definition started with a color atlas published in 1835. It was printed by the French dermatologist Pierre François Olive Rayer to illustrate his "Treatise on Skin Disease." One of the plates depicted a man's face dotted with "small vascular, of papulous appearance, widespread

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See also page 12.

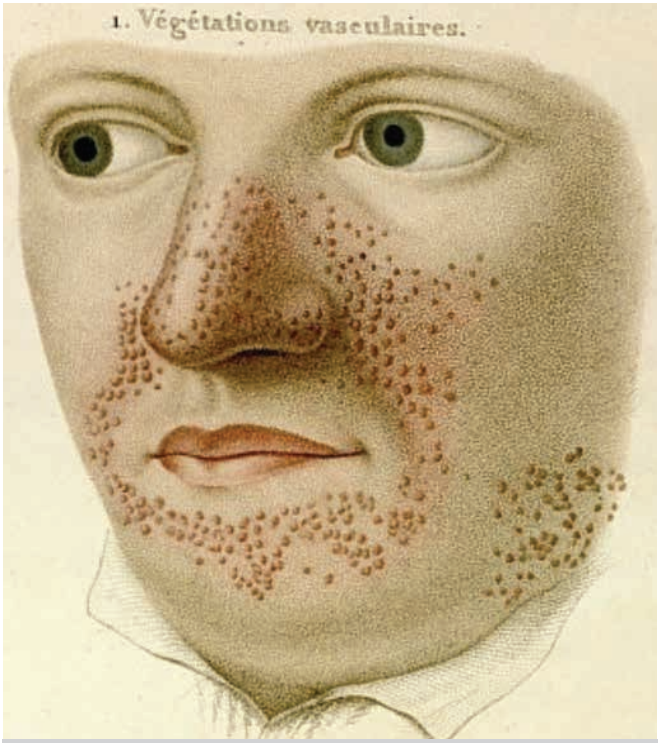

Figure 1. Végétations vasculaires image by Rayer (1835).

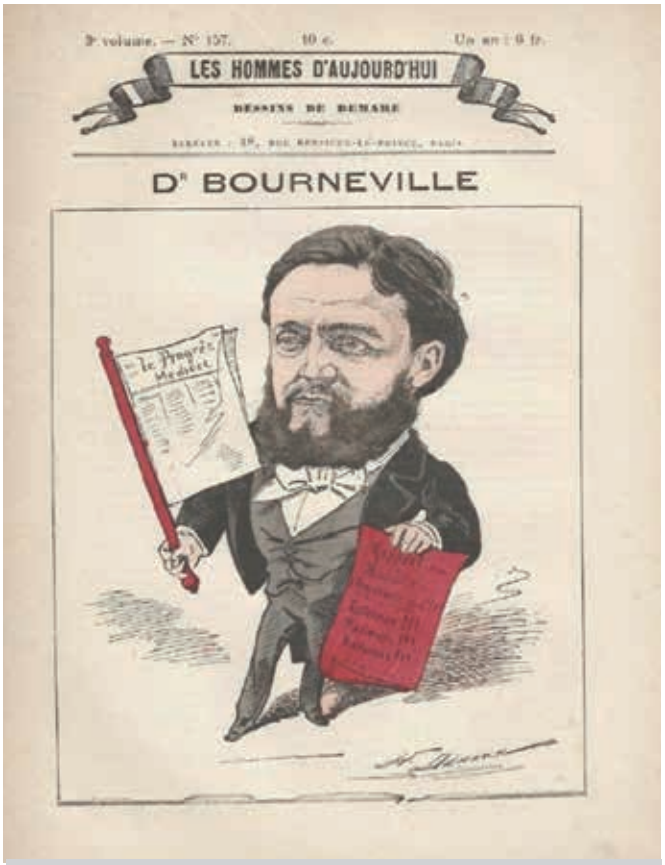

Figure 2. Désiré-Magloire Bourneville on Les Hommes d'Aujourd Hui No. 157.

growths distributed on the nose and around the mouth," termed *végétations vasculaires* (Figure 1).[3] Rayer, however, did not link his observation to other systemic signs. Fifteen years later, skin features of tuberous sclerosis were reported under the name of *vitiligoidea tuberosa* by Thomas Addison and William Gull, two Dermatologists from Guy's Hospital, London, who described a 4-year-old girl with a "peculiar eruption extending across the nose and slightly affecting both cheeks."[4]

STEPS TOWARD SYNDROME DEFINITION: THE LATE 19TH CENTURY

The first syndromic description of tuberous sclerosis was in 1862 when a young German physician, Friedrich Daniel von Recklinghausen, made a presentation to the Obstetrical Society of Berlin on the pathological findings of a newborn with several cardiac tumors, which he named *myomata*, who "died after taking a few breaths," and who had "a great number of scleroses" in the brain.[5] These were probably the first descriptions of TSC cardiac rhabdomyomas and cortical tubers. Von Recklinghausen was an assistant to the great anatomist Rudolf Virchow. Tuberous sclerosis history was destined to be deeply influenced by assistants of outstanding scientific personalities as he himself was. As a matter of fact, a seminal advancement in TSC definition must be credited to Desire-Magloire Bourneville. He was born in 1840 in Normandie, France. Although a cholera epidemic prevented him from completing secondary school, he entered the Paris Medical Faculty in 1860 on recommendation of Louis Jean Francois Delasiauve, an outstanding French psychiatrist who worked at the Bicêtre Hospital and who would become director at the Salpêtrière. Delasiauve was first a family friend and later one of Bourneville's mentors.[6] After graduating in Medicine, Bourneville became a pupil of Jean-Martin Charcot and was influenced by Noel Pascal, Claude Bernard, and his mentor Delasiauve at the Bicêtre Hospital.[7] Bourneville founded many scientific journals and exhibited the viewpoint of a medical reformist, best expressed in "*Le Progres Medical*" (Figure 2). In the period of the Third Republic, he was elected municipal councilor and then member of parliament for the extreme left wing party.[6] In May 1879, Bournville came across the history of tuberous sclerosis while he was in charge of Marie, a 15-year-old girl with psychomotor retardation, recurrent status epilepticus, and a "confluent vascular-papulous eruption of the nose, the cheeks

and forehead." Despite treatment with quinquina, bromide of camphor, amyl nitrite, and the application of leeches behind the ears, Marie died. Bourneville described the post-mortem examination as "sclérose tubéreuse des circonvolutions cérébrales" because of the white nodular tumors with potato-like firmness. These were embedded in the corpus striatum and protruded into the lateral ventricles he had found on sagittal sections of the brain. He also described kidney involvement, as hard whitish renal masses, one "the size of a walnut."[2] One year later, Bourneville and Brissaud described a similar cerebral pathology in a 4-year-old boy dead in status epilepticus (Figure 3).[7] Bourneville's work was so important that tuberous sclerosis would later become known as the Bourneville syndrome. The link with epilepsy was soon confirmed, accompanied by the description of cerebral periventricular tumors described as "glioma gangliocellulare cerebri congenitum" by Hartdegen[8] and the observation of renal angiomyolipomas.[7]

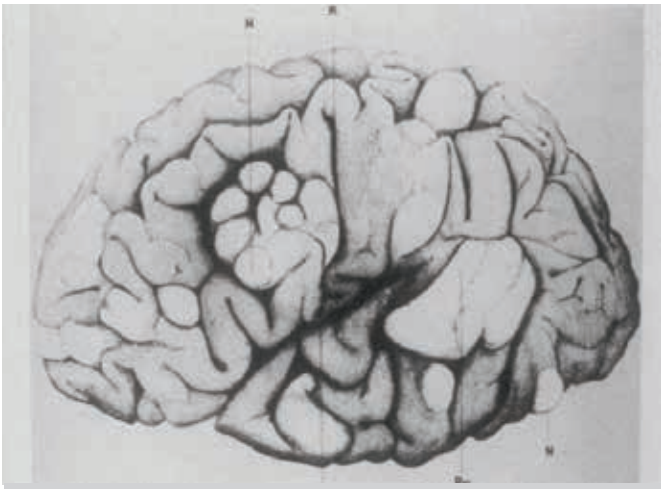

Figure 3. Sclérose tubéreuse des circonvolutions cérébrales (Bourneville and Brissaud, 1881).

LINKING THE SKIN TO THE BRAIN

In 1885, attention returned to facial appearance, when the French dermatologists Félix Balzer and Pierre Eugène Ménétrier described the association between cognitive impairment and facial dermatitis.[3] In the same period, Hallopeau and Leredde reported an association between facial dermatitis and epilepsy.[9] A few years later, John James Pringle used his dermatological expertise to define the syndrome. Pringle was born in Scotland in 1855 and had international medical training in Edinburgh, Vienna, and Paris. From 1883, he worked at the skin department of the Middlesex Hospital in London before becoming editor of the *British Journal of Dermatology* and president of the dermatology section of the *Royal Society of Medicine*. In 1890, Pringle described a case of tuberous sclerosis facial dermatitis, which would take the eponym *Pringle's adenoma sebaceum*, because it was thought to be a benign tumor of the sebaceous glands, although the skin lesions are actually angiofibromas.[7]

EARLY 20TH CENTURY: GOING DEEPLY INTO CEREBRAL PATHOLOGY

An outstanding advancement in the comprehension of cerebral neuropathology came from Giovanni Battista Pellizzi. He recognized the dysplasic nature of cortical tubers, which were of two types: type 1 (smooth surface) and type 2 (with central depressions). Moreover, he reported white matter abnormalities and neuronal heterotopia.[10] Pellizzi, former assistant to the famous Cesare Lombroso, published his findings as part of the essays on "idiozia" (mental retardation), for which he was granted the qualification of Director of the Neuropsychiatric Clinic and then Dean of the Faculty of Medicine at the University of Pisa, Italy.[11] A few years later, Gaetano Perusini, former pupil of Alois Alzheimer and an unacknowledged contributor to the discovery of the Alzheimer disease definition, reported on the microscopy of cortical tubers and noted the association of cerebral, renal, and cardiac lesions with facial angiofibromas. Parallel advancements came from dermatology, with the recognition of periungual fibromas.[7]

TIME FOR SYNDROME RECOGNITION: THE EARLY 20TH CENTURY

Dermatology and neurology eventually converged in the early 20th century. First, Alfred Walter Campbell suggested that the aforementioned characteristics were part of a single syndrome.[2] Then, the German neurologist Heinrich Vogt formally defined tuberous sclerosis and established a triad of diagnostic criteria—epilepsy, idiocy, adenoma sebaceum ("Vogt triad")—that would characterize the syndrome for decades thereafter.[12] Vogt's criteria were widely accepted but, unfortunately, they brought about the idea that the 3 features were mandatory. Hence, tuberous sclerosis was considered a severe and disabling condition with mental retardation and a tendency to family clustering.[13] People with tuberous sclerosis were depicted as "feeble-minded" and the term *epinoia*—epilepsy and anoia (mindless)—was coined.[4] Despite this common misconception, patients with normal intelligence were also described and defined as "forme fruste."[3]

A NEW CONCEPT: PHAKOMATOSES

Anecdotal reports of pathology in tissues different from brain and skin have already been mentioned. Nevertheless, in the

early 20th century, tuberous sclerosis was still regarded as an exclusively neurocutaneous disorder. It was in the 1920s that the concept of "phakomatoses" arose. First, René Lutembacher described a case of lung involvement (ie, lymphangioleiomyomatosis, a rare complication affecting only women). The Dutch ophthalmologist Jan van der Hoeve then observed retinal hamartomas, coining the term *phakoma* (from the Greek "phakos" meaning "mother spot") for congenital tumors arising in different tissues. He suggested that the syndromes of tuberous sclerosis, neurofibromatosis, and von Hippel-Lindau should be grouped as phakomatoses, having hereditary multisystem tumors with risk of malignant transformation in common.[3]

THE TSC

In the 1930s, main clinical investigations were conducted in mental institutions, with misrecognition of "forme fruste" and underestimation of tuberous sclerosis prevalence; however, asylums offered the chance of describing disease series. In 1932, MacDonald Critchley and Charles J.C. Earl described a comprehensive cohort, emphasizing for the first time the value of skin hypomelanotic macules as well as the presence of psychiatric disorders and autism.[7] The advent of pioneering neuroimaging increased the possibility of diagnosis: X-ray made the detection of intracranial calcified nodules possible and pneumoencephalography identified noncalcified subependymal.[14,15] It was time to widen the syndrome's definition. In 1942, Sylvan E. Moolten proposed "the Tuberous Sclerosis Complex" describing it in three concepts: "the basic lesion is hamartial, becoming, in turn, tumor-like (hamartoma) or truly neoplastic (hamartoblastoma)."[16]

CHALLENGING THE VOGT TRIAD

Despite the TSC definition, a quarter of century had to pass before new revolutionary ideas challenged the Vogt triad. The misconception of patients with TSC as unfortunate and mentally retarded still persisted. In 1967, J.C. Lagos and Manuel Rodríguez Gómez published a remarkable case series reporting that 38% of these patients had normal intelligence. Moreover, they observed that mental retardation was strictly associated with epilepsy.[17] In the meanwhile, Perot and Weir pioneered the first neurosurgical interventions of cortical tuber resection, and further studies led to a better definition of seizures in tuberous sclerosis.[18] It was once again the work by Gómez that marked a huge advancement in syndrome definition. Gómez was born in Spain and had a brilliant career that spanned from graduation in medicine at the Universidad de la Habana, Cuba, to studies in the United States and at the Institute of Neurology in London, until he became Professor of Pediatric Neurology at the Mayo Clinic, Rochester, in 1964. There he founded what would become the Division of Child and Adolescent Neurology at the Mayo Clinic School of Medicine.[19] In 1979, he published the monograph "Tuberous Sclerosis," the first and, for more 20 years, only textbook on the disease, in which he defined new diagnostic criteria.[20] The Tuberous Sclerosis Alliance established the Manuel R. Gómez Recognition Award in his honor in 1995.

THE NEW DIAGNOSTIC ERA

In the 1980s, dermatologic advancement ameliorated the care and the quality of life of patients with tuberous sclerosis. A disease stigmata, facial angiofibroma was successfully treated by argon laser in 1982.[21] In the meanwhile, infantile spasms had become a core feature and diagnostic evaluations of intracerebral lesions had progressed as a result of the recently discovered magnetic resonance imaging.[22,23] The number of cortical tubers was identified as a predictive factor for epilepsy severity and cognitive impairment.[24]

Finally, the phenotype spectrum had been described. The Vogt triad had been disproved, showing that epilepsy and cognitive impairment are not inevitable. Diagnostic advancements had allowed an early and reliable diagnosis. Nevertheless, syndrome etiology remained obscure, even though heritability had been observed since the early 20th century.

GENETICS ADVANCEMENT: THE LATE 20TH CENTURY TOWARDS THE FUTURE

It was the study of families that allowed the detection of a suspected genetic marker on chromosome 9—the TSC1 (9q34)—and on chromosome 16—the TSC2 (16p13.3).[25,26] Eventually, the TSC2 gene was identified in 1993, while the TSC1 gene wasn't identified until 1997.[27,28] These genes encode hamartin and tuberin, respectively. The syndrome was recognized as an autosomal-dominant disease with high penetrance and variability. Approximately two thirds of cases were identified as sporadic, resulting from de novo mutations. Mutations of TSC1 and TSC2 were considered as part of a "second hit" hypothesis: a somatic, second-hit mutation of TSC1 or TSC2 might synergize with "first-hit" systemic mutations of the same gene to cause complete loss of function. The second hit could occur in any tissue, leading to different clinical phenotypes. Several research groups investigated the function of tuberin and hamartin and discovered that they inhibit the mammalian target of the rapamycin (mTOR) pathway, which regulates cell proliferation and tumor suppression. Loss of these tumor suppressors leads to hamartomas as a result of heightened mTOR sig-

naling.[29] Currently, technological advancements allow genetic counseling and prenatal diagnosis. It is now acknowledged that people with TSC have a 50% risk of transmitting the disease to their offspring and that new mutation cases are common. In genetic counseling it is important to exclude parents' disease by physical examination and possibly by cranial computed tomography and renal ultrasound. For unaffected parents, the risk of another child with TSC is approximately 2% because of germline mosaicism. If the mutation can be identified in the index case, genetic testing can be offered to parents and siblings. In regards to prenatal diagnosis, it is currently possible to offer first-trimester chorionic villus sampling and molecular genetic diagnosis, echocardiography, and ultrafast brain magnetic resonance imaging.[30]

Table II. Revised Diagnostic Criteria for Tuberous Sclerosis Complex

Major features
- Facial angiofibromas or forehead plaque
- Nontraumatic ungal or periungal fibromas
- Hypomelanotic macules (≥3)
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber(s)
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma, single or multiple
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor features
- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter "migration tracts"
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- "Confetti" skin lesions
- Multiple renal cysts

Modified from Roach and Gómez & Northrup, 1998: Definite tuberous sclerosis complex: 2 major features or 1 major plus 2 minor features. Probable tuberous sclerosis complex: 1 major feature plus 1 minor feature. Possible tuberous sclerosis complex: 1 major feature or ≥2 minor features. Clinical signs once regarded as pathognomonic are now not considered mandatory. Based on new findings, the disease spectrum has been widened. No single sign is present in all affected patients, and there is no proof that any single clinical or radiographic sign is absolutely specific for tuberous sclerosis complex.

CONCLUSIONS

Tuberous sclerosis is now considered an autosomal-dominant neurocutaneous disorder characterized by hamartomas in multiple organs. Updated diagnostic criteria have been established based on the acknowledged variable clinical manifestations (Table II).[31] At present, the management of tuberous sclerosis is symptomatic; however, as a result of genetic findings, new possibilities of treatment are under investigation, especially drugs that interfere with the mTOR pathway (eg, rapamycin and everolimus). One hundred seventy-eight years after Rayer's plate, many steps have been made but the history of tuberous sclerosis is still to be completed.

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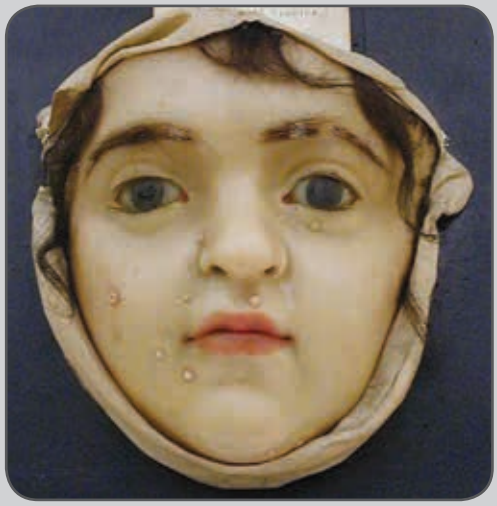

Chickenpox: Courtesy of Museo delle Cere Anatomiche L. Cattaneo, University of Bologna, Italy. Photo by Cristian Mancini. Submitted by Diana Garrisi, London, UK.

Edward L. Keyes Resident Contest for Outstanding Case Reports

10th World Congress of the International Academy of Cosmetic Dermatology
Rio de Janeiro, Brazil, November 14–16, 2015
Abstract deadline: June 1st, 2015

To be awarded for the best Case Report submitted by a physician in training (resident, fellow, or registrar) for presentation at the 10th World Congress of the International Academy of Cosmetic Dermatology in Rio de Janeiro, Brazil, November 14–16, 2015.

We invite you to submit original Case Reports that reflect the presentation of new ideas and original observations to the Academy membership and other attendees of the Congress. The case may be medical, surgical, cosmetic, or combined in nature. The author whose abstract receives the highest score during the review process will be awarded a scholarship by the IACD to present the full paper at the 10th World Congress of the International Academy of Cosmetic Dermatology in Rio de Janeiro, Brazil, November 14–16, 2015. The scholarship will provide reasonable travel expenses, lodging for 3 nights, the Congress registration fee, and a basic spending stipend.

Abstracts should be submitted via email to vrosic@medicine.bsd.uchicago.edu before noon, CDT, August 16th, 2015 and should be no longer than 2,500 characters including spacing. Material that was previously presented, published, or submitted for publication should not be offered. Applications will be graded based upon the educational value of the abstract and the extent to which it presents new and significant work. The Review Committee strongly recommends that abstracts have an organized, coherent, well-thought-out, and complete presentation. The winner(s) will publish their outstanding case report(s) in *SKINmed: Dermatology for the Clinician*, an official publication of the International Academy of Cosmetic Dermatology.

All applicants will receive e-mail notice of the Resident Case Report Review Committee's decision by September 15th, 2015.

Vesna Petronic-Rosic, MD, MSc
Chair, Resident Contest Committee
Associate Professor
The University of Chicago Pritzker School of Medicine,
Section of Dermatology
Tel: +1.773.702.6559
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Official publication of IACD

CASE STUDY

Vesna Petronic-Rosic, MD, MSc, Section Editor

Autologous Fat Transplantation for the Treatment of Linear Scleroderma en Coup de Sabre

Kristina S. Ibler, MD;[1] Christina Gramkow, MD;[2] Peter A. Siemssen, MD[2]

Scleroderma en coup de sabre is a disfiguring disease for which only limited therapeutic options exist. Three cases of facial linear scleroderma treated with autologous fat transplantation with acceptable results are presented. Autologous fat transplantation was preferred to corrective surgery because of the extent of the lesions and absence of any associated facial distortion. Fat as a filler was chosen to reduce the risk of adverse effects. Adipocytes are suggested to have wider biological effects than other fillers and may offer more durable results. At least two transplantations were needed to evoke a significant effect. (*SKINmed.* 2015;13:74–76)

Scleroderma en coup de sabre is a disfiguring disease for which only limited therapeutic options exist.[1] The disease has two distinct phases: an early inflammatory phase and a subsequent phase in which sclerosis of the skin is predominant. Treatments described as effective are mostly directed at the inflammatory phase of the disease and include systemic treatments such as methotrexate and corticosteroids.[2,3] For very superficial and early lesions, topical tacrolimus has also been suggested to be effective,[4] while the treatment options for sclerotic lesions are limited to phototherapy using UV-A–1, psoralen–UV-A (PUVA), or narrowband UV-B.[5,6] For stable disease, surgical correction of facial asymmetry is possible, either by traditional surgery or the use of fillers; however, the data are sparse.[7] We present 3 cases of facial linear scleroderma treated with autologous fat transplantation with acceptable results.

CASE 1

A 28-year-old man insidiously developed a linear, hyperpigmented vertical lesion in the midline of the forehead, running from the hairline to the nose. The lesion presented as a hyperpigmented, shiny, firm streak of fibrotic tissue. There were no signs of generalized disease or neurological abnormalities. Based on the characteristic clinical presentation, the patient underwent UV-A–1 irradiation a total of 28 times (35 J/cm^2) unsuccessfully. The patient was referred to the department of plastic surgery, and autologous fat transplantation was performed twice within 10 months. A total of 7.5 mL of fat was transplanted. One year after the second treatment, improvement of the contour difference was found, but hyperpigmentation of the scar remained. Intense pulsed light therapy (IPL) (10 ms, 32 J/cm^2) was tried once in the upper part of the lesion, but the hyperpigmentation was unchanged and no further treatments were given.

CASE 2

A 28-year-old woman presented with a linear, sagittal lesion on the right side of the forehead, running from the hairline across the forehead to the cheek, without involvement of the eye (Figure 1). Localized scleroderma was also present in the lumbar region as circular indurated, shiny, slightly hyperpigmented and firm lesions. There were no signs of generalized disease or neurological abnormalities. The lesion on the forehead was treated with UV-A–1 (35 J/cm^2) 40 times. According to the patient, the UV-A–1 treatments had a softening effect on the lesion; however, no effect of the treatment was found by the attending physician. The patient was referred to the department of plastic surgery, and autologous fat transplantation was performed twice within 12 months. A total amount of 23 mL of fat was transplanted. The result was excellent after 1 year, including improvement of the hyperpigmentation (Figure 2). Two years after the second transplantation, the scleroderma reoccurred. A third autologous fat transplantation will be considered in the future, when the lesion is stable.

From the Department of Dermatology[1] and Department of Plastic and Reconstructive Surgery,[2] Roskilde Hospital, Health Sciences faculty, University of Copenhagen, Denmark

Address for Correspondence: Kristina S. Ibler, MD, Department of Dermatology, Roskilde Hospital, Køgevej, DK-4000 Roskilde, Denmark • E-mail: ksi@regionsjaelland.dk

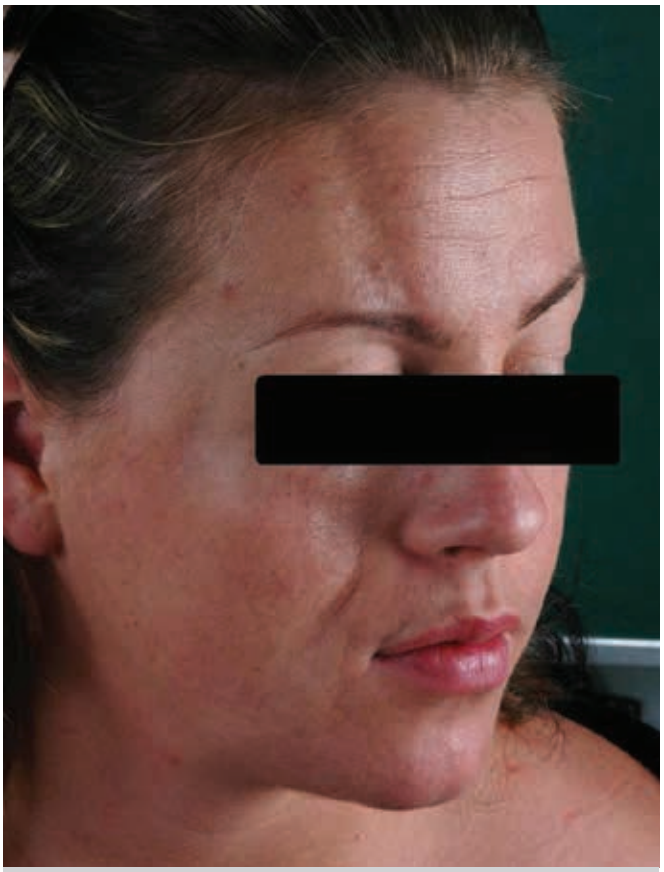

Figure 1. Before autologous fat transplantation.

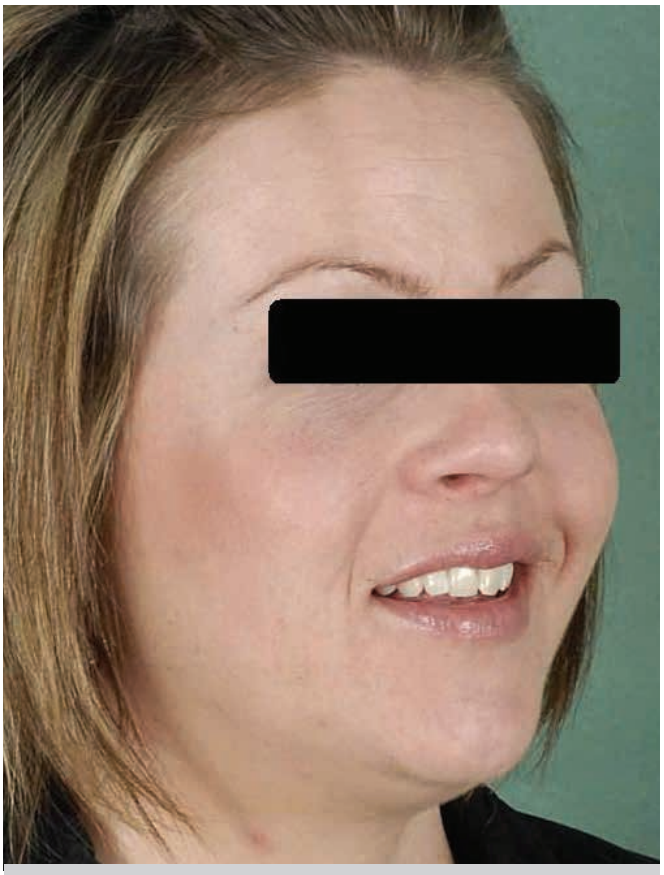

Figure 2. After autologous fat transplantation.

CASE 3

A 22-year-old woman developed a deep, linear, saggital, hyperpigmented, and firm lesion on the left side of the forehead, running from the hairline to the eyebrow. The patient had endocrinological comorbidity (myxoedema, polycystic ovary syndrome, hirsutism) and was treated with levothyroxin and biguanid, of which none were related to scleroderma. Based on the characteristic clinical presentation and absence of systemic sclerosis, the patient was consecutively treated with calcipotriol, tacrolimus, and 50 UV-A–1 treatments (35 J/cm^2) but with no clinical improvement. The patient was referred to the department of plastic surgery, and autologous fat transplantation was performed twice within 12 months. A total amount of 5 mL of fat was transplanted. Improvement was found of the contour difference, and a softening effect on the surrounding tissue and scar was also observed. The hyperpigmentation improved only slightly.

DISCUSSION

In the present cases, treatment with localized autologous fat transplantation was chosen because of the absence of inflammation and systemic complications. The use of fat as a filler was preferred to corrective surgery because of the extent of the lesions and absence of any associated facial distortion. A range of fillers is available for corrective procedures, but autologous fat transplantation was chosen. The choice was made based on two considerations. Firstly, the volume of tissue that needed to be replaced was considerable in all 3 cases. The injection of large volumes of permanent artificial filler increases the risk of an adverse effect.[8] Secondly, data suggest that transplanted adipocytes may have wider biological effects than other fillers, eg, hyaluronic acid, and may offer a more durable solution to the patient.[9] The mentioned cases were all treated with the fat grafting technique.[10] In general anesthesia, donor sites (abdominal fat) were infiltrated with Klein's formula containing saline, lidocaine, and a vasoconstrictor,[11] and fat was harvested and refined. Purified fat was transferred to 1-mL syringes and injected as microdroplets, and the lacking tissue was built up in a 3-dimensional plane with a slight overcorrection. To preserve the contour of the region, local anesthetics were avoided in the treated areas. Blunt cannulas were used to avoid damage to vessels and nerves. Postoperative complications included only minimal bruising and

edema. Clinical examination and photography took place 3, 6, 9, and 12 months after the operation.

Our data support previous findings of an improving effect of the use of autologous fat transplantation in patients with linear scleroderma en coup de sabre.[12,13] At least two transplantations were needed to evoke a significant effect. The immediate benefits of the treatments were a more even contour of the depressed areas of the lesions and improvement in skin quality and surrounding soft tissue. Adipose-derived stem cells may provide an explanation for the surface feature improvements and may reflect an additional benefit of the treatment over the use of artificial or passive fillers. The biological activity of transplanted adipocytes has been suggested to be useful in the treatment of other atrophic or fibrotic conditions such as radiation dermatitis and breast capsular contracture.[14]

Not all issues were solved by autologous fat transplantation. The postinflammatory hyperpigmentation of the lesions persisted even after surgery. IPL treatment (10 ms, 36 J/cm^2) was tried in one case but with no effect on the hyperpigmentation. Bleaching creams, chemical peeling, and laser resurfacing were not tried in the cases and may be helpful in removal of hyperpigmentation.

CONCLUSIONS

Treatment efficacy was evaluated by Physician's Global Assessment of Clinical Condition and patient assessment alone. No other validated outcome measures were used such as ultrasound measurements. In future studies, efficacy should be measured by use of validated methods such as The Localized Scleroderma Cutaneous Assessment Tool,[15] which is a newly developed clinical tool, and patient-centered information such as quality-of-life measures.

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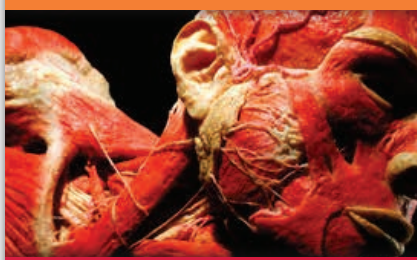

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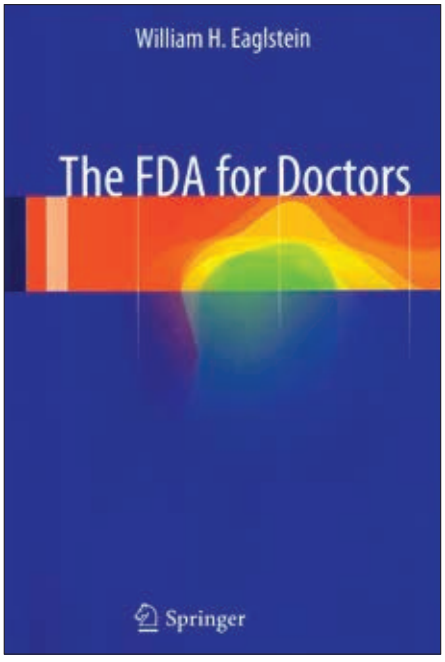
BOOK REVIEW

Jennifer L. Parish, MD, Section Editor

The FDA for Doctors

By William H. Eaglstein, New York, NY: Springer; 2014: Pages 97. $79.99

The Food and Drug Administration (not the Federal Drug Agency), better known as the FDA (not FD&A), is a powerful agency under the Executive Branch of the Federal Government, being one of the 11 agencies controlled by the Department of Health and Human Services (HHS). Its mission is to protect consumers and enhance "public health by maximizing compliance of FDA-regulated products and minimizing risk associated with those products" (see www.fda.gov). The mandate includes foods and drugs, with its purview ranging from tobacco to human and veterinary agents.



THE AUTHOR

The author is eminently qualified to write such a work. Dr Eaglstein was Chief of Dermatology at the University of Pittsburgh School of Medicine before becoming Chairman of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine. More recently, he served in the capacity of scientific liaison for a major pharmaceutical company. During his career, he has been intimately involved in the development of new dermatologics and their place in the clinic.

THE FDA

How did such a massive agency that employs more than 15,000 employees and controls a budget exceeding $4.5 billion come into being? This is an excellent book that explores the question and provides many more details about the FDA.

During the presidency of Theodore Roosevelt, there was a public outcry against the terrible conditions commonplace in the meat industry. The muckrakers spurred this on; most notable among them was Upton Sinclair who wrote *The Jungle*. Dr Harvey W. Wiley (1844–1930), Chief Chemist for the Department of Agriculture, campaigned against food adulteration and for truth in labeling of foods, so much so that for many years after Congress passed the Pure Food and Drugs Act in 1906, it was referred to as the Wiley Act. The bureau later became known as the Food, Drug, and Insecticide Administration before assuming its current name.

The next major change was an outgrowth of the S. E. Massengill scandal of 1937. Sulfonamides had recently been introduced to the pharmacopeia, and the Bristol, TN, company wanted to make a liquid form that would appeal to children. Unfortunately, the chemist used antifreeze for formulating the tincture. There were more than 100 deaths from this fiasco that resulted in Congress giving the agency more power.

In 1962, the Kefauver-Harris Amendment was passed, which required new drugs to show efficacy before being marketed. This change was instigated by the thalidomide debacle. Although the sleeping pill was being marketed in several European countries, the FDA had not yet approved it for the United States. Dr Francis Kelsey, as the FDA reviewer, repeatedly delayed approval of thalidomide, because she could not find enough information about the drug's thyroid toxicity status. During this interval, reports of phocomelia began to appear in Germany, where the

Reviewed by Lawrence Charles Parish, MD, MD (Hon), Clinical Professor of Dematology and Cutaneous Biology, Director of the Jefferson Center of International Dermatology, Sidney Kimmel Medical College at Thomas Jefferson University, 1845 Walnut Street, Suite 1650, Philadelphia, PA 19103 • E-mail: larryderm@yahoo.com

drug, Contergan, was being marketed for morning sickness in pregnant women. Fortuitously, only a few cases of babies with absent limbs appeared in the United States, and this was the result of women importing the drug on their own.

Today, the FDA has jurisdiction over several areas:

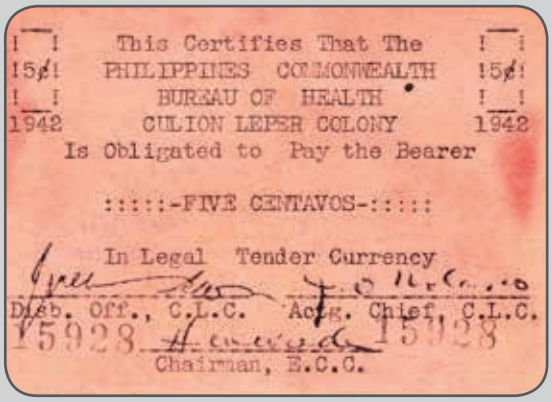
- "Protecting the public health by assuring that foods (except for meat from livestock, poultry and some egg products which are regulated by the U.S. Department of Agriculture) are safe, wholesome, sanitary and properly labeled; ensuring that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use are safe and effective
- Protecting the public from electronic product radiation
- Assuring cosmetics and dietary supplements are safe and properly labeled
- Regulating tobacco products
- Advancing the public health by helping to speed product innovations" (from http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194877.htm).

The FDA does not regulate the practice of medicine; licensing is done by individual states. In addition, the FDA cannot limit the individual physician from using a medicament, as its purview involves interstate commerce. If an agent is made in the same state where the physician practices, it is not a matter for the FDA.

RECOMMENDATION

There are additional fascinating revelations and accounts given in this succinct volume. The physician, to whom this book is directed, will learn about the regulatory process for drugs and how devices differ from drugs, nutraceuticals, and cosmeceuticals, just to list a few areas of discussion. Dermatologists will find this book to be a fascinating excursion into another part of contemporary medicine.

VINTAGE LABEL



Courtesy of Lawrence Charles Parish, MD, MD (Hon)

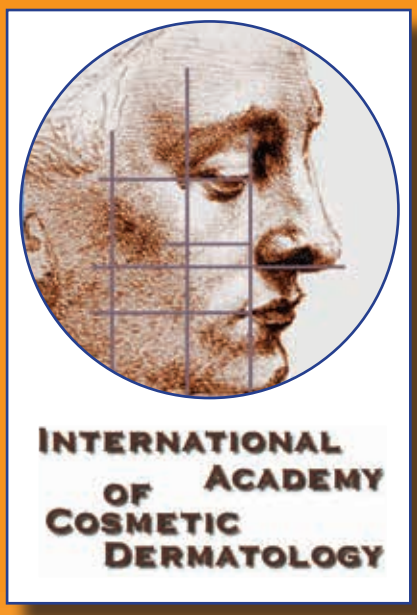
ADDENDUM

SKINmed. 2014;12:322.

Ackerman's Dictionary of Dermatohistology and Dermatolohistopathology

Vesna Petronic-Rosic, MD, MSC

Subsequent to the publication of the Book Review for Steffen C: *Ackerman's Dictionary of Dermatohistology and Dermatolohistopathology*, an on-line version of the book has become available at http://charlessteffenmd.com/Terms___Definitions.html.



GREAT EXPECTATIONS

THE GOOD VS. THE BAD, AND THE UGLY

Monday Morning, 8 am–12 noon, June 8th 2015
Vancouver Convention Centre – Room # West 210

Jennifer L Parish, MD, Director
Philadelphia, Pennsylvania, USA

The Good will focus on what new treatments and techniques that are available and also on new ideas with old treatments and techniques.

The Bad and The Ugly will focus on complications and procedures that do not provide significant results.

Co-chairs: To be announced

8:00-8:09 Introduction
Jennifer L Parish, MD

8:10-8:34 Scars

The Good
1 Esperanza Welsh, MD: Monterey, Mexico
Scars: Treatment with Lasers, Fillers, Cryotherapy, and Beyond

The Bad and The Ugly
2 Oliverio Welsh, MD: Monterey, Mexico
Scars: Cryochemopeeling in Acne and its Sequelae

8:35-8:59 Hair Transplantation

The Good
3 Walter Unger, MD, FRCPC: Toronto, Ontario, Canada
Hair Transplantation 2015: the Good News

The Bad and The Ugly
4 Robin Unger, MD: Toronto, Ontario, Canada
Hair Transplantation: New Innovations and their Potential Pitfalls

9:00-9:24 Drugs

The Good
5 Zoe Draelos, MD: High Point, North Carolina, USA
Beneficial Skin Cosmetics

The Bad and The Ugly
6 Larry Millikan, MD: Meridian, Mississippi, USA
Drugs and their Reactions

9:25-9:49 Injections

The Good
7 Hassan Galadari, MD: Dubai, United Arab Emirates
Mid Face Augmentation with New Innovations for Treating the Tear Trough

The Bad and The Ugly
8 Doris Hexsel, MD: Porto Alegre, Brazil
Complications of Fillers in the Mid and Lower Face

9:50-10:14 Pigmentary Disorders

The Good
9 Almond Derla, MD: Manila, the Philippines
Pigmentation Disorders: New Treatments and Techniques

The Bad and The Ugly
10 Mysore Venkataram, MD: Bangalore, India
Complications of Vitiligo Treatment and other Pigmentary Disorders

Health Break 10:15-10:29

10:30-10:54 Beautiful Inside and Out

The Good
11 Marina Landau, MD: Holon, Israel
The Science and Art of Chemical Peels

The Bad and The Ugly
12 Uwe Wollina, MD: Dresden, Germany
Adverse Events with Fillers and Tattoos – the Bad and Ugly Side

10:55-11:19 Promises and Myths of Beauty Treatments

The Good
13 Kyle Coleman, MD: Austin, Texas, USA
New Treatments and Techniques for Body Sculpting

The Bad and The Ugly
14 Vesna Petronic-Rosic, MD, MSc: Chicago, Illinois, USA
Myths and Facts about Sensitive Skin

11:20-11:44 Mohs Surgery

The Good
15 Paul Benedetto, MD: Philadelphia, Pennsylvania, USA
What is New in Mohs Surgery?

The Bad and The Ugly
16 Anthony Benedetto, DO: Philadelphia, Pennsylvania, USA
Mohs: What Went Wrong?

11:45-12:00 Discussion and Awards for the most persuasive speakers

The Good vs. The Bad and The Ugly

IMPORTANT INFORMATION ABOUT

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BRIEF SUMMARY

This summary contains important information about MIRVASO (Mer-VAY-Soe) Gel. It is not meant to take the place of the full Prescribing Information. Read this information carefully before you prescribe MIRVASO Gel. For full Prescribing Information and Patient Information please see package insert.

WHAT IS MIRVASO GEL?

MIRVASO (brimonidine) Topical Gel, 0.33% is a prescription medicine that is used on the skin (topical) to treat facial redness due to rosacea that does not go away (persistent).

WHO IS MIRVASO GEL FOR?

MIRVASO Gel is for use in adults ages 18 years and older.

WHAT WARNINGS AND PRECAUTIONS SHOULD I BE AWARE OF?

MIRVASO Gel should be used with caution in patients that:

- have depression
- have heart or blood vessel problems
- have dizziness or blood pressure problems
- have problems with blood circulation or have had a stroke
- have dry mouth or Sjögren's Syndrome
- have skin tightening or Scleroderma
- have Raynaud's phenomenon
- have irritated skin or open sores
- are pregnant or plan to become pregnant. It is not known if MIRVASO Gel will harm an unborn baby.
- are breastfeeding. It is not known if MIRVASO Gel passes into breast milk. You and your female patient should decide if she will use MIRVASO Gel or breastfeed. She should not do both.

Ask your patient about all the medicines they take, including prescription and over-the-counter medicines, skin products, vitamins and herbal supplements. Using MIRVASO Gel with certain other medicines may affect each other and can cause serious side effects.

Keep MIRVASO Gel out of the reach of children.

If anyone, especially a child, accidentally swallows MIRVASO Gel, they may have serious side effects and need to be treated in a hospital. Get medical help right away if you, your patient, a child, or anyone else swallows MIRVASO Gel and has any of these symptoms:

- **Lack of energy, trouble breathing or stops breathing, a slow heart beat, confusion, sweating, restlessness, muscle spasms or twitching.**

WHAT ARE THE POSSIBLE SIDE EFFECTS OF MIRVASO GEL?

The most common side effects of using MIRVASO Gel include:

- redness, flushing, burning sensation of the skin, skin irritation

Skin redness and flushing may happen about 3 to 4 hours after applying MIRVASO Gel. Ask your patients to tell you if they get skin redness and flushing that is uncomfortable.

MIRVASO Gel can lower blood pressure in people with certain heart or blood vessel problems. See **"What warnings and precautions should I be aware of?**"

These are not all of the possible side effects of MIRVASO Gel. Remind your patients to call you for medical advice about side effects.

You are also encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

HOW SHOULD MIRVASO GEL BE APPLIED?

- Remind your patients to use MIRVASO Gel exactly as you instruct them. They should not use more MIRVASO Gel than prescribed.
- Patients should not apply MIRVASO Gel to irritated skin or open wounds.
- **Important**: MIRVASO Gel is for use on the face only. Patients should not use MIRVASO Gel in their eyes, mouth, or vagina. They should also avoid contact with the lips and eyes.
- Instruct your patients to see the detailed Instructions for Use that come with MIRVASO Gel for information about how to apply MIRVASO Gel correctly.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF MIRVASO GEL

Remind your patients not to use MIRVASO Gel for a condition for which it was not prescribed and to not give MIRVASO Gel to other people, even if they have the same symptoms. It may harm them.

WHAT ARE THE INGREDIENTS IN MIRVASO GEL?

Active Ingredient: brimonidine tartrate
Inactive Ingredients: carbomer homopolymer type B, glycerin, methylparaben, phenoxyethanol, propylene glycol, purified water, sodium hydroxide, titanium dioxide.

WHERE SHOULD I GO FOR MORE INFORMATION ABOUT MIRVASO GEL?

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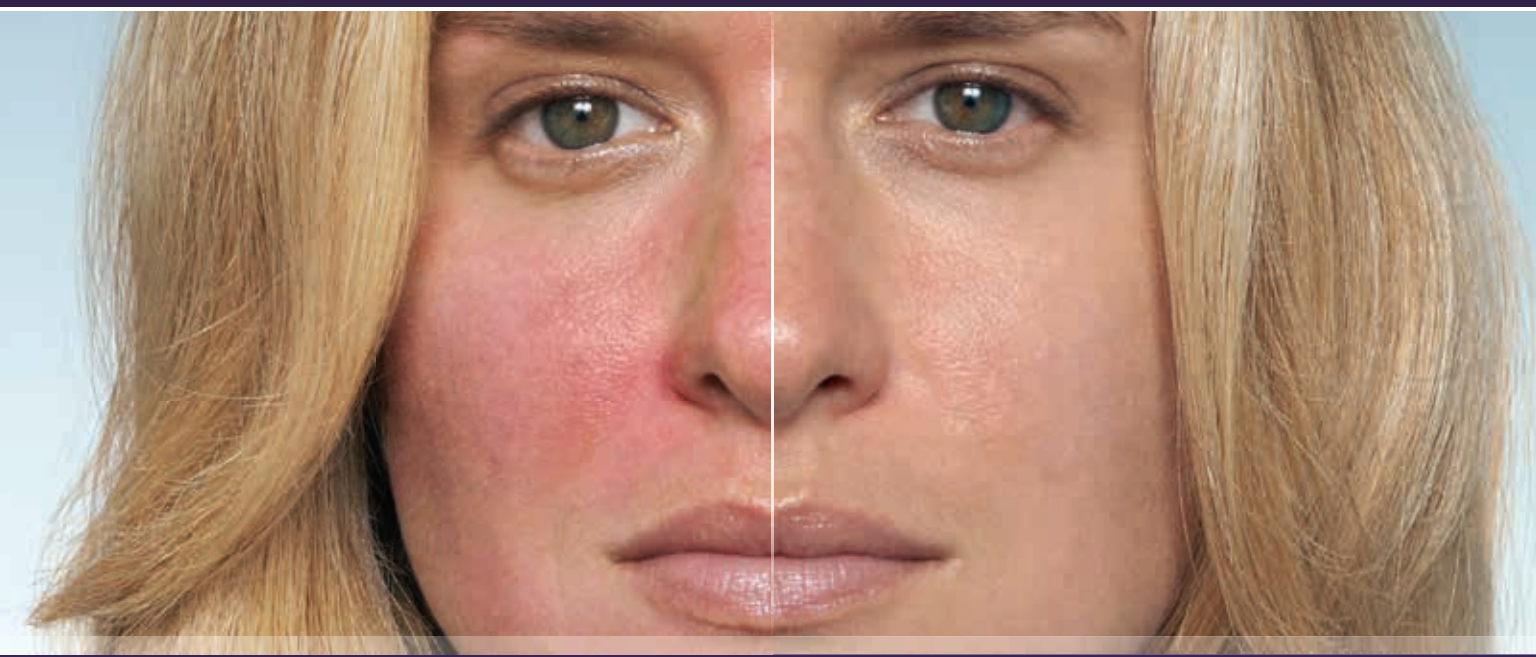
GALDERMA Committed to the future of dermatology

References: 1. Fowler J Jr, Jackson JM, Moore A, et al; Brimonidine Phase III Study Group. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. *J Drugs Dermatol.* 2013;12(6):650-656. **2.** Mirvaso [package insert]. Galderma Laboratories, L.P. Fort Worth, TX; 2013.

Help your patients with facial erythema of rosacea experience...

THE MIRVASO EFFECT



Not an actual patient. Individual results may vary. Results are simulated to show a 2-grade improvement of erythema. At hour 12 on day 29, 22% of subjects using Mirvaso Gel experienced a 2-grade improvement of erythema compared with 9% of subjects using the vehicle gel.*

RAPID AND SUSTAINED ERYTHEMA REDUCTION BROUGHT TO YOU BY MIRVASO® (brimonidine) TOPICAL GEL, 0.33%†

- The **first** and **only** FDA-approved topical treatment specifically developed and indicated for the facial erythema of rosacea[1]
- Fast results that last up to **12 hours**[1]
- The most commonly reported adverse events in controlled clinical studies included erythema (4%), flushing (2%), skin-burning sensation (2%), and contact dermatitis (1%)[2]

Important Safety Information

Indication: Mirvaso® (brimonidine) topical gel, 0.33% is an alpha-2 adrenergic agonist indicated for the topical treatment of persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older. **Adverse Events:** In clinical trials, the most common adverse reactions (≥1%) included erythema, flushing, skin-burning sensation, and contact dermatitis. **Warnings/Precautions:** Mirvaso Gel should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome. Alpha-2 adrenergic agents can lower blood pressure. Mirvaso Gel should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease. Serious adverse reactions following accidental ingestion of Mirvaso Gel by children have been reported. **Keep Mirvaso Gel out of the reach of children.** Not for oral, ophthalmic, or intravaginal use.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit *www.fda.gov/medwatch* or call 1-800-FDA-1088.

Please see brief summary of full Prescribing Information on the following page.

See for yourself. Visit **www.mirvaso.com/hcp**.

MIRVASO®
(brimonidine) topical gel, 0.33%

*Phase 3 clinical studies of 553 subjects 18 and older. Subjects were randomized 1:1 to either Mirvaso Gel or vehicle for 29 days. Subjects and clinicians were asked to grade the improvement they saw at 30 minutes and hours 3, 6, 9, and 12 following application.

†Each gram of gel contains 5 mg of brimonidine tartrate equivalent to 3.3 mg of brimonidine free base.