The Mitochondria and Complex II—Linchpin for Skin Aging and Photoaging

Mitochondria are far more than the power plants of our cells. Few people realize that these tiny structures play a central role in our physiology in various contexts and maintain a complex, synergistic relationship with the nuclear genome (see box on page 2). Molecular dermatology scientist Mark A. Birch-Machin, PhD, is among those who do. (Birch-Machin is Professor of Molecular Dermatology; Department of Dermatology; Associate Dean, Newcastle University Institute of Cellular Medicine; Newcastle University, Newcastle upon Tyne, England.)

And in studying the functions of mitochondria in human skin, Birch-Machin recently made an eye-opening discovery that is critically important to both mitochondrial and skin health in chronologic and photoaging. It concerns the unexpected protective role of complex II—the diminutive, unassuming member of the respiratory enzyme chain that completes conversion of the energy from glucose into ATP (see box on page 7). The implications are profound for understanding what can go wrong and why, and for developing therapeutic interventions to slow chronological aging, protect against photoaging, and reverse existing changes of concern.

Getting Hooked on Mitochondria—And Then the Skin

When Birch-Machin finished his PhD in molecular biology in 1986, he chose a postdoctoral fellowship with mitochondrial expert Professor Sir Doug Turnbull at Newcastle University in the U.K. Turnbull—now Director of the Wellcome Trust Centre for Mitochondrial Research there—was dedicated to uncovering the molecular mechanisms responsible for mitochondrial diseases. “I was very much impacted by the illnesses associated with mitochondrial dysfunction,” Birch-Machin recalls. “Children with these diseases died very early, and it was devastating.” He has been committed to understanding mitochondrial dysfunction ever since, with the ultimate goal of finding ways to correct it.

For the next decade Birch-Machin focused on pediatric mitochondrial myopathies, with assignments in the U.S., Canada, and then Paris. Along the way, he began to develop innovative techniques for gaining information about the mitochondrial genome. Then, while he was at the Hôpital Necker for Sick Children in Paris, the Department of Dermatology at Newcastle University expressed interest in having him apply his research techniques to mitochondria in human skin.

As he considered this, Birch-Machin began to think about the skin’s role of “communicating with the environment—and I had a kind of epiphany,” he recalls. “I knew from my mitochondrial research in muscle and brain that mitochondria play a role in chronologic aging, which involves declining (Continued on page 2)
metabolic energy and increasing oxidative stress. I also knew that mitochondria don’t repair very well,” he continues—“and it occurred to me that mitochondrial damage in the skin most likely increases measurably with sun exposure. I became really excited to study the role of mitochondria in skin aging, and also understand the effect that sun exposure has on this normal process. In my experience, no one had explored this before—and I wanted to do it.” Birch-Machin has focused on the skin ever since, expanding understanding in ways that will ultimately influence patient care.

**mtDNA Damage—Biomarker of Cumulative UV Radiation Exposure**

Specific properties of the mitochondrial genome had led Birch-Machin to hypothesize that mtDNA damage accurately reflects the cumulative impact of sun exposure. Mitochondrial genes lack the histone covering that is an important protector of nuclear genes, and their repair mechanisms are limited. The genome is also in close physical proximity to where superoxide generation—which occurs during UV exposure—takes place. So the mitochondrial genome is multiply vulnerable, and its limited repair capabilities allow damage to accumulate over time. The extent of this underlying damage, though, is not manifest. Because there are a great many nonclonal mitochondria within individual cells and multiple copies of the mitochondrial genome within each mitochondrion (see box below), there are usually enough molecules of functional mtDNA to compensate for those with mutations and maintain cell functions. But Birch-Machin suspected that assessing the extent of these silent mutations should provide measurable evidence of UV-induced damage to mtDNA, and that the extent of damage would increase with increasing UV exposure—ie, it would be a highly sensitive biomarker of UV exposure in human skin.

Previous studies had examined the frequency of just a single common deletion. But Birch-Machin believed that a complete picture was the only accurate way to begin. He and his team assessed 71 split-skin samples taken from body areas that were either unexposed, intermittently exposed, or highly sun exposed, and identified the full spectrum of mtDNA deletions in each skin sample. The number of deletions in the epidermis increased significantly as UV exposure increased, but mtDNA in the dermis showed no effect. Next, they focused on a single, rarely reported 3895 bp mtDNA deletion in age-matched skin samples, again from body areas with large differences in sun exposure. The frequency of this rare deletion increased in line with increasing UV exposure—this time in both the epidermis and dermis. Exposing cultured human fibroblasts to a UVA+UVB light source confirmed this. The same rare mtDNA deletion appeared; then its presence increased in response to continued exposure.

Next, Birch-Machin and his team determined that the shorter UVR wavelengths (>320 nm) are primarily responsible for this mtDNA damage—the same part of the spectrum already implicated in both UVR-induced erythema and nuclear DNA damage in the skin. Under shorter-wavelength UVR, dermal fibroblasts turned out to be far more sensitive to

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**Mitochondria—The Tiny Organelles with the Huge Punch**

Back in the mists of evolutionary time, our mitochondria—the cellular organelles in our cytoplasm that produce 90% of the chemical energy that our cells need to survive, and contribute substantially to other basic cellular functions—were independently dwelling purple photosynthetic bacteria. As eukaryotes evolved more than 1 billion years ago, these free-living bacteria became incorporated within them—the process of endosymbiosis—and developed a mutually dependent relationship. Their genomes, though, remained independent entities, and mitochondrial replication is independent of cell division. The human nuclear genome now contains 3 billion base pairs, with only about 2% actually coding for its 20,000 genes. The mitochondrial genome (mtDNA) evolved in the opposite direction, contracting down to a 16.5-kb circular structure containing just 16,569 base pairs and 37 genes (see illustration on front cover). Unlike nuclear DNA, mtDNA is a model of efficiency, with no introns and no spacing between genes, so that almost all of it (~93%) represents a coding region. These dual-membrane mitochondria are rich in fats, proteins, and enzymes, but some of the proteins essential to their function—including the entire complex II respiratory enzyme (see box on page 7)—are produced by the cell, not by the mitochondria.

What this genome lacks in size, it makes up for in exceptional numbers. Excluding mature red blood cells, which are unique in lacking both a nucleus and mitochondria, the individual cellular presence of these organelles ranges from around 1,000 in cells with lower ATP needs to roughly 7,000 in individual human myocytes. Adding it all up, we contain roughly 500 trillion mitochondria, accounting for roughly 30% of our body weight. And each individual mitochondrion holds from 1 to 15 mtDNA molecules. Each cell’s population is not clonal, but includes normal—ie, wild-type—and various mutation-altered states. The presence of wild-type genomes is potent. “There can actually be quite profound deficiencies and damage present, but the remaining wild-type genomes will complement the damaged ones,” Birch-Machin explains. “In some cases, just 10% of the mitochondrial genomes need to be normal to make up for the deficiencies of the other 90%.”

Although mitochondria are best known as the cell’s powerhouse—converting the energy from glucose into ATP—this is just part of what they do. Among other things, they participate in cellular differentiation, cell growth, the cell cycle, apoptosis, and steroid synthesis. They are platforms for intracellular signaling, regulators of innate immunity, modulators of stem cell activity, and are host to numerous biosynthetic and signaling processes that ultimately couple cellular metabolism to homeostatic regulatory mechanisms. Dysfunctional mitochondria are thus responsible for a number of human diseases and conditions. This past summer, mitochondrial research at the University of Southern California documented cross-regulation between the nuclear and mitochondrial genomes—noting that sometimes it’s the mitochondrial DNA in charge.
sun-induced mtDNA damage than keratinocytes, a discovery that holds "important implications for disease and photodamage mechanisms and for interventions," Birch-Machin points out.

Complex II—Newly Recognized Importance in Skin

The four respiratory chain enzymes—complex I through complex IV—gradually transform the energy from glucose into ATP (see box on page 7). The byproducts of this process also make these enzymes the major generator of cellular oxidative stress. mtDNA vulnerability to this stress results in damage that in turn reduces the mitochondria’s ability to repair themselves, which increases the production of mutations and dysfunction, which further increases ROS production, which diminishes repair capabilities still further, producing additional mutations. This vicious cycle is thought to underlie the mitochondria’s contribution to aging, cancer, neurodegeneration, and cell death in many tissues.

Birch-Machin and his group had already shown that UVA exposure increases both ROS production and mtDNA mutations in human skin. Now he wanted to begin exploring its role in this vicious cycle by identifying the most important sites of ROS production within the mitochondrial respiratory chain. Although he was not the first investigator to pose this question, he was among the very few to explore it in skin and the first to pursue it in human skin. Birch-Machin found this lack of attention to human skin quite surprising, "given that the skin is regularly exposed to the harmful UVA rays in sunlight."

He and his team created multiple cultures of human keratinocytes (from the immortalized HaCaT cell line) and of fibroblasts (from neonatal foreskin). Each of the four respiratory chain enzymes can be inhibited by several chemical agents, and Birch-Machin modified the individual cultures by adding, separately, each of these inhibitors. Then he exposed these cultures to doses of UVA irradiation that are comparable with normal outdoor exposure. Representative cultures were left unexposed as controls. The expectation was that among the various UVA-exposed cultures, the missing enzyme associated with the largest drop in UVA-induced ROS production would—under normal circumstances—be the largest contributor to ROS production.

The results took them in a very different direction. Complex II stood out—but not for producing the lion’s share of ROS. Instead, it was unique for its ability to suppress ROS production, because inhibiting its activity increased ROS levels considerably.

Birch-Machin also engineered a comparison of young and aging tissues to see if the levels of these respiratory chain enzymes change with age. Shrinking telomeres are considered to be a biomarker of aging, so he and his team used cultures grown from two versions of human fetal lung fibroblasts. The "youthful" tissue cultures were grown from fibroblasts engineered to overexpress the telomerase enzyme, which lengthens telomeres at the ends of nuclear genes. Because the unaltered—wild-type—cells had shorter telomeres, in relative terms they represented aging tissue. Assessing the individual levels of complexes I–IV in the "young" and "aging" fibroblast cultures highlighted complex II again. It was the only respiratory chain enzyme showing decreased activity in the "aging" lung fibroblasts. In line with this, recent data from a lab using mice to study aging skin in vivo had shown a decrease in complex II activity along with an increase in senescent cells in the skin as mice aged.

Birch-Machin realized for the first time that "the effect of complex II in human skin cells may be significantly more important than previously thought." It would explain why the activity of this tiny enzyme is approximately twofold greater in skin cells than in the liver, for example. Complex II also differs

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from the other three respiratory chain enzymes in a fundamental way. All of its subunits and assembling proteins are produced exclusively by the nuclear genome.

Pursuing the Aging Connection
Birch-Machin wasted no time in following up on this observation that “younger” fetal lung fibroblasts contained more complex II than the “older” ones did. “It is highly important to understand the aging process in skin,” he emphasizes. “Skin is the largest organ of the body, acting as a protective barrier to a spectrum of external insults that includes UV radiation, infection, toxicity, and mechanical stress.” A better understanding of the underlying biology will enable maintenance of skin health. And beyond this, “the skin is an organ that can be accessed and studied easily, and thus what is learned from this research may have profound relevance and application to aging in other body tissues,” he adds.

To explore the role of complex II in skin aging, Birch-Machin and his team worked with foreskin tissue (sun-protected, eliminating any influence of UV exposure) from 27 males ranging from 6 to 72 years of age. They studied skin aging from two perspectives. Biological aging concerns the functional decline of the entire organism over time. Cellular senescence involves the transformation of proliferating cells to a state of irreversible growth arrest. On the positive side, senescence acts as an important tumor suppressive mechanism by preventing potentially malignant cells from undergoing replication; plus, senescent cells produce cytokines that aid wound healing. But senescent cells also have a number of significant negative effects—including ROS production and secretion of inflammatory cytokines—and thus are thought to be prominent in the aging process.

Biological aging: Birch-Machin and his team cultured fibroblasts and keratinocytes from each of these skin samples, then precisely calculated the activity level of complex II per unit of mitochondria in every culture. They also measured gene transcript expression and protein levels for complex II.

Continued on page 6
Dr. Callen notes that teaching has always held special meaning for him. “It is deeply rewarding because of the reach I have,” he explains. “I love taking care of patients—but when I am in my office my reach is limited to the individual patient. When I’m sharing information that will help others be effective dermatologists, I hope to improve the quality of a great many patients’ lives.”

Ironically, Dr. Callen had planned to follow in his cardiologist father’s footsteps. He was enjoying his final year of internal medicine residency at the University of Michigan and eagerly anticipating a cardiology fellowship when his dermatology rotation began. “I was seeing patients who had challenging problems that related a great deal to internal medicine,” he recalls, “and this experience was fascinating.” Then Dr. Callen learned that there would be a new dermatology chair and a position was open for residency. He was encouraged to apply—and was accepted. “It was not an easy decision to give up that cardiology slot, but I had been smitten by the complexity of dermatology and the visual ability to make diagnoses,” he says. “I was in the right place at the right time.”

Dr. Callen points out that “my interest from the start was this intersection between the external and the internal.” He has shared what he has learned in what have become definitive texts: *Dermatological Signs of Systemic Disease*, and *Color Atlas of Dermatology*. One of Dr. Callen’s special authorial enjoyments is unearthing dermatology-relevant information in the nondermatology literature and reviewing it for the dermatology community.

An exceptional number of official accolades over his career attest to Dr. Callen’s profound influence on the field as one of the specialty’s outstanding clinicians, scientists, organizational thought leaders, and teachers. His recent selection by the AAD for the *Master Dermatologist* award also emphasizes his “extraordinary and vast contributions through curriculum development and authorship of hundreds of publications.”

Over the years, Dr. Callen has been instrumental in training and teaching thousands of students and colleagues. One colleague’s comment says it all: “Quite simply, Dr. Callen has changed my life as a physician, educator, and mentor. He has single-handedly changed our field for the better—and his impact will continue for generations to come.”

### 2019 Leadership Gala

The Annual Leadership Gala is always eagerly anticipated by *Leaders Society*, *Annenberg Circle*, *AC Sustaining*, and *Fitzpatrick Legacy Fund* members. The DF provides this special thank-you for their strong, ongoing commitment to advancing the knowledge that is essential to progress in patient care.

This year’s Gala, and the Young Leaders Pre-Gala, were held the evening of March 3 at Washington DC’s memorable National Museum of Women in the Arts.

The DF is grateful to the co-sponsors of this memorable event: *Celgene Corporation*; *Galderma*; *Lilly USA, LLC*; *Ortho Dermatologics*
Results were compared with complex IV, chosen as the control because—unlike complexes I and III—it is not directly linked to complex II within the electron transport chain. When the results were in, it became clear that complex II activity is pivotal to fibroblast function—but not to keratinocytes.

To begin with, complex II activity was substantially greater in fibroblasts than in keratinocytes, up to twice as high in cell cultures from younger donors. In addition, complex II activity decreased steadily with donor age—but only in fibroblasts (see graphs below). Because gene transcript expression and protein levels for complex II also declined with age in fibroblasts, it appeared that in fibroblasts from this sun-protected area, the enzyme itself had not lost effectiveness with age but there was less and less of it. With the increasing loss of complex II’s protective actions, ROS-caused damage would exacerbate this diminishing activity. Complex IV showed no relation to age in either cell culture.

Senescence: When Birch-Machin and his team turned their attention to the relationship between senescence, complex II, and biological age in human skin, the results shed light on their observations with biological aging. Fibroblast cultures from 15 of the initial donors (ages 6–71 years) were separated into senescent and nonsenescent cell populations using the senescence biomarker lipofuscin, a wear-and-tear fluorescent pigment that is a remnant of the transition to senescence. As donor age increased, the number of senescent fibroblasts increased while the activity level of complex II decreased—but only in senescent fibroblasts. (Complex IV activity level in senescent fibroblasts was unrelated to donor age.)

Fibroblasts

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Keratinocytes

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Complex II pivotal to fibroblasts. In foreskin samples from males ranging from 6–72 years of age, complex II activity was highest in fibroblasts from the youngest donors and steadily decreased with age. There was no relationship in keratinocytes from these same samples. (Reprinted with permission from A Bowman & MA Birch-Machin. J Invest Dermatol. 2016;136:912–19.)
age.) The surprise was that purely nonsenescent fibroblast cultures showed no correlation between aging and complex II activity. These unexpected results refocused the initial picture. The age-related decrease in complex II activity observed in the original fibroblast cultures did not actually reflect the entire fibroblast population, but was specifically a function of the senescent cell subset. Isolating the senescent fibroblasts for study emphasized that—in terms of mitochondrial complex II activity—senescent fibroblasts in the skin of older individuals are less efficient than those in younger individuals.

Human in vivo data will be required to confirm and flesh out the role of decreasing complex II activity in skin aging, and to clarify whether this loss is a cause or a consequence of aging—or both, as the vicious cycle of aging would predict. Any of these scenarios,

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including direct DNA damage initiated by increased ROS production, is likely to increase overall mitochondrial dysfunction. And the result is decreased tissue function.

**Testing Interventions**

Because antioxidant compounds neutralize ROS, thus reducing or eliminating oxidative damage, this is a logical area to explore for candidates to support skin health and prevent further damage in the face of ROS-inducing conditions. Birch-Machin has begun evaluating candidates from medicinal plants and plant extracts as well as chemical molecules.

**Clitoria ternatea L:** Birch-Machin learned of *C. ternatea*—the butterfly pea plant—from Dr. Edward Okello, a neurology colleague who is also Executive Director of the Medicinal Plant Research Group. Indigenous to tropical Asia, the plant spread more widely across Asia and to Latin America and the East and West Indies, and has extensive traditional uses. One involves an herbal tea made from the colorful blue-and-white flower that is taken to protect the skin against age-related changes and sun-induced damage. Research on the plant’s biological activities have focused on the root, seeds, and leaf, but the flower was recently found to contain anthocyanins, which are known antioxidants.

Birch-Machin incubated human keratinocyte cultures with the flower water extract (CTW), then rinsed them before exposure to hydrogen peroxide or UV. There was significantly less cytotoxicity and mtDNA damage after CTW treatment than in nontreated cells. A phytochemical analysis of the flower identified major concentrations of polyacylated anthocyanins and flavonol glycosides, both with widely documented antioxidant actions. Birch-Machin points out that the flower extract’s significant ability to protect against UV-induced mtDNA damage indicates a potential for preventing oxidative stress arising from mitochondrial dysfunction. Further research for therapeutic benefits is warranted. “We will also be studying additional Malaysian species, working in conjunction with Kew Gardens in London,” Birch-Machin says.

**Antioxidant molecules:** The first round of experiments compared the protective capability of two antioxidant molecules able to penetrate the mitochondria. *MitoQ* (mitoquinone)—a modified ubiquinone molecule developed

(Continued on page 10)
“Thank You” to 2018 Leaders Society Volunteers

The DF Board of Trustees extends special appreciation to every one of these national campaign volunteers. They have each invested significant work to increase leadership giving in their area. Their concern for continued progress in patient care, and their gift of time and effort throughout 2018, helped to expand support for advancement in the specialty.

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*Enrolled three or more new LS members
by Mike Murphy, PhD, Program Leader of the MRC Mitochondrial Biology Unit, University of Cambridge, UK—is actively and exclusively attracted to mitochondria, and sufficiently small to penetrate the mitochondrial membrane. *Tiron* is a mitochondria-permeating and localized superoxide scavenger and antioxidant and also chelates metals (including iron and titanium). Human fibroblast cultures were incubated with one or the other, then exposed to physiologic doses of UVA or to hydrogen peroxide. Tiron completely prevented ROS-induced mtDNA damage across the board. MitoQ reduced damage by 17% and 32%, respectively. (For UVA, see graphs at left.)

Birch-Machin suspected that Tiron’s complete elimination of ROS production indicated a protective effect extending beyond the mitochondria, and further exploration also demonstrated complete protection of the nuclear genome from hydrogen peroxide-induced damage. MitoQ achieved 18%. Birch-Machin showed that these effects are completely independent of the Nrfl2-signaling pathway.

(Continued on page 14)
CHART A COURSE TO SYMPTOMATIC RELIEF

The efficacy of Class 1 halobetasol with safety proven for up to 8 weeks of dosing\(^1\)\(^2\)

STUDY RESULTS: 36.5% of patients in trial 1 and 38.4% in trial 2 achieved treatment success* at week 8 (primary endpoint) vs 8.1% and 12.0% of patients with vehicle, respectively (\(P<0.001\) in both trials)\(^3\)

STUDY DESIGN: The safety and efficacy of BRYHALI Lotion were assessed in 2 prospective, multicenter, randomized, double-blind, phase 3 clinical trials in 430 adult patients with moderate-to-severe plaque psoriasis. Patients were treated with BRYHALI Lotion or vehicle lotion, applied once daily. Primary efficacy endpoint was treatment success evaluated at week 8. Secondary efficacy endpoint was treatment success evaluated at weeks 2, 4, 6, and 12 (4 weeks post treatment). Tertiary efficacy endpoint was a 2-grade improvement from baseline at each time point for the individual signs of psoriasis (erythema, plaque elevation, and scaling)\(^2\)

* Treatment success was defined as at least a 2-grade improvement from baseline in the Investigator’s Global Assessment score, and a score of “clear” or “almost clear” (primary endpoint at week 8)\(^4\)


Indication
BRYHALI\(^\text{TM}\) (halobetasol propionate) Lotion, 0.01% is a corticosteroid indicated for the topical treatment of plaque psoriasis in adults.

Important Safety Information
Warnings and Precautions
• BRYHALI Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during treatment or upon cessation of treatment; periodic evaluation may be required.
• Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and glucosuria.
• Children may be more susceptible to systemic toxicity when treated with topical corticosteroids.
• Local adverse reactions may include atrophy, striae, telangiectasias, hypopigmentation, and allergic contact dermatitis. Some local adverse reactions may be irreversible.
• Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist.
• Use an appropriate antimicrobial agent if a skin infection is present or occurs, and if prompt response is not seen, discontinue use until infection has been adequately treated.
• Discontinue BRYHALI Lotion if allergic contact dermatitis occurs.

Adverse Reactions
• The most common adverse reactions (≥1%) were upper respiratory tract infection, application site dermatitis, and hyperglycemia.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or FDA at 1-800-FDA-1088.

Please see Brief Summary of full Prescribing Information on following page.
INDICATIONS AND USAGE

Initial U.S. Approval: 1990

This brief summary does not include all the information needed to use BRYHALI safely and effectively. See full prescribing information for BRYHALI.

BRYHALI™ (halobetasol propionate) lotion, 0.01% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

BRYHALI has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticoid insufficiency. This may occur during treatment or upon withdrawal of treatment with the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with BRYHALI was evaluated in a study of 19 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area (BSA). HPA axis suppression was reported for 1 (5.6%) subject at Week 4 and for 3 (15.8%) subjects at Week 8. All 3 subjects had normal HPA axis suppression test with discontinuation of treatment [see Clinical Pharmacology in full Prescribing Information].

Because of the potential for systemic absorption, use of topical corticosteroids, including BRYHALI, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to corticosteroids. Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios [see Use in Specific Populations].

Local Adverse Reactions

Local adverse reactions from topical corticosteroids may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermartitis, allergic contact dermatitis, secondary infection, and miliaria. These reactions are generally more frequent with the more potent corticosteroids. The risk of these reactions may be reduced by using the least potent drug effective for the patient’s condition and by using the vehicle with the lowest possible concentration effective for the patient’s condition. Although atrophy, striae, and miliaria may be irreversible, they have usually been reversible upon discontinuation of treatment with topical corticosteroids.

Concomitant Skin Infections

Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of BRYHALI until the infection has been adequately treated.

Allergic Contact Dermatitis

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Consider confirmation of a clinical diagnosis of allergic contact dermatitis by appropriate patch testing. Discontinue BRYHALI if allergic contact dermatitis occurs.

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 directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 426 adults with plaque psoriasis were treated with BRYHALI and had post-baseline safety data. Subjects applied BRYHALI once daily for up to eight weeks. Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with BRYHALI and more frequently than in vehicle-treated patients.

Table: Adverse Reactions Occurring in ≥1% of the Subjects Treated with BRYHALI through Week 8

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BRYHALI (N=284)</th>
<th>Vehicle (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Application Site Dermatitis</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on BRYHALI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rats and rabbits. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of BRYHALI. The background risk of major birth defects and miscarriage in the clinically recognized population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Halobetasol propionate has been shown to cause malformations in rats and rabbits when given orally during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

Lactation

Risk Summary

There are no data on the presence of halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with BRYHALI.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BRYHALI and any potential adverse effects on the breastfed child from BRYHALI.

Clinical Considerations

Advise breastfeeding women not to apply BRYHALI directly to the nipple and areola to avoid direct infant exposure.

Pediatric Use

Safety and effectiveness of BRYHALI in pediatric patients under the age of 18 years has not been evaluated.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing’s syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children [see Warnings and Precautions].

HPA axis suppression, Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema [see Warnings and Precautions].

Geriatric Use

Of 284 subjects exposed to BRYHALI in clinical trials, 61 subjects were 65 years or older. Clinical trials of BRYHALI did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, or in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vitro and in a Chinese hamster microcosmic test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day indicated no impairment of fertility or general reproductive performance.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Manufactured for:

Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC

Bridgewater, NJ 08807 USA

BY:

Valeant Pharmaceuticals International, Inc.

Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,017,847 and 8,809,307

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Based on 9652102 November 2018 BRY.0032.USA.18

Hyperglycemia 1% 0
## New Leaders Society Members Invest in Progress

The DF Board of Trustees is pleased to recognize the Leaders Society members who joined their colleagues in 2018 to invest $1,500 annually to further the advancement of knowledge and patient care in dermatology. The Foundation appreciates their confidence in its ability to identify and support the research that will drive this progress for years to come.

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*Italics = Young Leader (5 years or less out of residency)*
which is known to provide cellular protection against oxidative stress.

Tiron completely abrogated mitochondrial and nuclear DNA damage in human skin cells exposed to these stressors. “We postulated that these profound in vitro antioxidant effects are attributable to the combination of its antioxidant and metal-chelating properties,” Birch-Machin explains. “It targets not just the ROS, but also the increased free intracellular metals that are released due to oxidative insults.” This points to the ideal therapeutic strategy of combining compounds with complementary capabilities.

Conclusions

It had first been speculated in the early 1970s that mitochondria play a key role in the aging process. Birch-Machin’s research in the skin “brings us one step closer to understanding how mitochondria may be contributing to this, with the hope of eventually targeting areas of the mitochondria in an attempt to counteract the signs of aging,” he states. This includes his search for a way to maintain ideal levels of complex II as an endogenous ROS suppressor, and his continuing work using Tiron as a preventive.

He is also expanding his pursuit of mtDNA involvement in skin health and disease. He is looking at mtDNA in the context of treating psoriasis, in the relationship between oxidative stress, nutritional status, and skin aging, and in the science and use of sunscreens.

Birch-Machin, though, is not mitochondria-centric. “The fascination and beauty for me,” he explains, “is the way the two genomes communicate and affect each other. Those who focus on just one of them and ignore the other—it’s at their peril,” he adds. “Our perspective should be a healthy balance between the two, as they are equally important.”

Suggested Readings


Coming in the Next Issue

• Highlights of the recent DF Annual Meeting
• Proceedings—Part I: summarizing the 2019 Clinical Symposia

Special Gifts for Advancing Patient Care

Tribute and Honoraria contributions are an effective, but often overlooked, way to support research through the Dermatology Foundation and enable the expansion of knowledge that is the foundation of improvements in clinical care.

Tribute Contributions: A meaningful way to increase the DF’s capacity for funding deserving research projects is by memorializing or honoring someone important to you—a family member, special friend, or mentor.

Honoraria: A unique way to make your member contribution this year is by arranging to have your honoraria paid directly to the DF. All such contributions to the DF are deeply appreciated, and help maintain the momentum of research and clinical progress in dermatology. For more information on contributing gifts of this kind, please call the DF office at 847.328.2256.
The Dermatology Foundation is grateful to the following corporations for their generous contributions last year. Their support furthers the DF’s ability to fund innovative research that shapes the future of dermatology.

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The DF Welcomes New President: Janet A. Fairley, MD

The Dermatology Foundation is pleased to announce the Board of Trustee’s election of Janet A. Fairley, MD, to serve as its new president. Dr. Fairley has been a member of the DF for over 30 years, and an active volunteer for nearly as many. She has contributed her outstanding leadership and perspective to a variety of DF fundraising, research award, and educational programs, including co-chairing the annual DF Clinical Symposia.

Dr. Fairley has been the John S. Strauss Professor and Chair of the Department of Dermatology at the University of Iowa since 2007. She is also a physician-scientist whose research activities have focused on the autoimmune blistering diseases. One of her major goals has always been to translate findings from the laboratory into improved diagnostics and/or therapies for patients.

Chairman Bruce U. Wintroub, MD, warmly welcomed Dr. Fairley to her new role. He added his sincere thanks to outgoing president Kim B. Yancey, MD, for his strong leadership as he completed his term at the Annual Meeting of Membership in Washington, DC.