DEFINING THE FUTURE OF DERMATOLOGY

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Medical Management of Skin Disease: Recent Advances and Future Directions

Whitney P. Bowe MD, Sharon Glick MD, Alan R. Shalita MD

State University of New York Downstate Medical Center, Department of Dermatology, New York, NY

Many dermatological conditions are amenable to medical management, and fundamental knowledge regarding the risks and benefits of such medical treatment remains pertinent for the vast majority of practicing dermatologists.

As we know, dermatology involves a broad range of diseases affecting pediatric through geriatric age groups, and ranging from inherited disorders characterized by genetic abnormalities to acquired disorders such as skin cancer and photoaging.

As dermatologists, we treat metabolic abnormalities as well as infectious diseases ranging from sexually transmitted diseases to *Staphylococcus aureus* (*S. aureus*) abscesses. Our knowledge regarding the structure and function of the skin, in addition to the role of the immune system and underlying genetic factors that predispose to disease continues to grow at an exponential rate. This knowledge will, without a doubt, continue to translate into novel medical therapies. Almost every disease manifesting on the skin can be treated with medical management, and such therapies are traditionally considered first-line.

Topical medications provide the benefits of local therapy while minimizing systemic toxicity. One example of the continuing evolution of topical medications can be seen in the medical management of atopic dermatitis.

Steroids and topical nonsteroidal medications (including tacrolimus and pimecrolimus) still remain cornerstones of atopic dermatitis therapy. More recent advances in this field include topical formulations designed to improve barrier function, receiving FDA approval as devices rather than drugs (e.g., EpiCeram skin barrier emulsion, Promius Pharma, Bridgewater, NJ). In the ubiquitous dermatological disease, acne vulgaris, similar advances in topical therapeutics are seen. Specifically, technological advances have resulted in more aesthetically pleasing topical formulations and combination products, resulting in decreased side effects and increased compliance. A deeper understanding of the human innate immune system has resulted in the development of topical immunomodulators (e.g., imiquimod) that aid in the treatment of precancerous and viral lesions. Current advancements in our understanding of antimicrobial peptides and antioxidants will likely translate into future topical formulations for prevention and treatment.

When dermatological disease becomes widespread, or is accompanied by systemic symptoms, a number of systemic medications prove beneficial. Given the chronic nature of many dermatological conditions—such as acne, rosacea, lupus, psoriasis and pemphigus—dermatologists are faced with the challenge of effectively treating diseases while minimizing the long-term sequelae of such treatment. Sustained-release and enteric formulations of oral medications have resulted in fewer doses per day, fewer side effects and, consequently, increased compliance. Although antibiotic resistance will continue to be an ongoing challenge, the medical community is attempting to combat these issues with more appropriate use of antibiotics combined with shorter duration of therapy. Furthermore, we have learned to harness the anti-inflammatory properties of certain drugs without predisposing to resistance (e.g., subantimicrobial dose doxycycline). Lastly, new purposes for old oral medications are being explored; propranolol has transformed the way we treat infantile hemangiomas.

Therapeutic advances based on our understanding of the genetic pathogenesis of disease have been increasing in recent years. One example includes the use of rapamycin, an mTOR (mammalian target of rapamycin) inhibitor, in tuberous sclerosis. Tuberous sclerosis (TS) is caused by inactivating mutations in the tumor suppressor genes hamartin (TSC1) or tuberin (TSC2). Hamartin and tuberin interact as a complex to suppress mTOR. In the absence of the normal function of this complex, the overexpression of mTOR leads to tumor formation of the CNS, kidneys, lungs, bone and angiofibromas of the skin.

Oral rapamycin therapy has shown efficacy in tumor regression in TSC-related tumors. Side effects include hyperlipidemia, immunosupression, impaired wound healing, oral ulceration and acneiform rash. Duration of therapy is another unresolved issue. In order to minimize systemic side effects, topical therapy has been developed and shown to be effective and well tolerated for the treatment of facial angiofibromas in a single patient. Larger clinical trials will be necessary in order to confirm the efficacy and safety of this exciting treatment.

A second example is the use of small interfering RNAs (siRNAs) for therapeutic applications in the dominant negative disorders. Pachyonychia congenital (PC), a keratin disorder characterized by a severe palmoplantar keratoderma, is caused by mutations in keratins 6A or 16 (PC-1) or keratins 6B or 17 (PC-2). SiRNAs can be constructed to specifically target and degrade the mu-

tated mRNA transcripts and suppress protein translation thus allowing for selective translation of the normal allele. This model has already proven successful in a limited trial for PC and is the prototype for treatment of other dominant negative genetic diseases.

Current and future challenges also involve medicolegal repercussions associated with using powerful systemic agents in the treatment of cutaneous disorders (isotretinoin). Dermatologists should not allow the fear of legal repercussions to take precedence over the implementation of evidence-based medicine. Our patients' needs must always come first, and in a litigious climate, this will continue to be an ongoing battle.

In summary, even with the advent and popularity of laser, surgical and cosmetic treatments, medical management of dermatological conditions remains the flagship of our therapeutic armamentarium.

DISCLOSURES

Dr. Shalita is a consultant for Allergan, Galderma, Graceway, Ortho Dermatologics, Medicis and Stiefel (GSK).

Dr. Glick is the principal investigator for the following study: A Randomised, Controlled, Multidose, Multicentre, Adaptive phase II/III Study in Infants With Proliferating Infantile Hemangiomas Requiring Systemic Therapy to Compare Four Regimens of Propranolol (1 or 3 mg/kg/day for three or six months) to Placebo (Double Blind). 2009 – Present.

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ADDRESS FOR CORRESPONDENCE

Whitney P. Bowe, MD
SUNY Downstate Medical Center
Department of Dermatology
P.O. Box 46
Brooklyn, NY, 11203
E-mail: ..... wpbowe@gmail.com