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Sugar Sag: Glycation and the Role of Diet in Aging Skin

Harrison P. Nguyen, BA and Rajani Katta, MD

Department of Dermatology, Baylor College of Medicine, Houston, TX, USA

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ABSTRACT

First described in the context of diabetes, advanced glycation end products (AGEs) are formed through a type of non-enzymatic reaction called glycation. Increased accumulation of AGEs in human tissue has now been associated with end stage renal disease, chronic obstructive pulmonary disease, and, recently, skin aging. Characteristic findings of aging skin, including decreased resistance to mechanical stress, impaired wound healing, and distorted dermal vasculature, can be in part attributable to glycation. Multiple factors mediate cutaneous senescence, and these factors are generally characterized as endogenous (e.g., telomere shortening) or exogenous (e.g., ultraviolet radiation exposure). Interestingly, AGEs exert their pathophysiological effects from both endogenous and exogenous routes. The former entails the consumption of sugar in the diet, which then covalently binds an electron from a donor molecule to form an AGE. The latter process mostly refers to the formation of AGEs through cooking. Recent studies have revealed that certain methods of food preparation (i.e., grilling, frying, and roasting) produce much higher levels of AGEs than water-based cooking methods such as boiling and steaming. Moreover, several dietary compounds have emerged as promising candidates for the inhibition of glycation-mediated aging. In this review, we summarize the evidence supporting the critical role of glycation in skin aging and highlight preliminary studies on dietary strategies that may be able to combat this process.

Key words: AGEs, advanced glycation end products, collagen, dietary sucrose, fibroblasts, nutrition, skin aging

Background: Glycation and Aging Skin

Societal obsession with the process of aging dates back to ancient history, and myths related to the conservation of youth–ranging from a bathing fountain that confers eternal youth to a philosopher's stone that could be used to create an elixir of life–populate both past and contemporary folklore. However, it is only within recent years that aging has been investigated from an empirical approach, as it continues to garner increasing attention from the scientific community. While several hypotheses have been proposed to explain the pathophysiology responsible for senescence, no single theory accounts for the diverse phenomena observed. Rather, aging appears to be a multifactorial process that results from a complex interplay of several factors and mechanisms.

Nevertheless, stratification of factors and mechanisms contributing to senescence is critical for the development of initial strategies in combating the aging process. The skin is an excellent paradigm for studying aging, in large part due to its easy accessibility. Moreover, in addition to its vulnerability to internal aging processes because of its diverse role in cellular processes, such as metabolism and immunity, the skin is subject to a variety of external stressors as the chief barrier between the body and the environment.

Aging factors can generally be classified as exogenous or endogenous. As ultraviolet (UV) radiation exposure is so strongly associated with a host of age-related skin diseases, endogenous and exogenous factors can theoretically be studied somewhat independently in the skin by differentiating between UV-protected and UV-exposed sites.[1] Endogenously aged skin displays characteristic morphological features with resultant alterations in functionality. These include epidermal, dermal, and extracellular matrix atrophy leading to increased fragility, diminished collagen and elastin resulting in fine wrinkle formation, and marked vascular changes disrupting thermoregulation and nutrient supply. Endogenously aged skin also displays decreased mitotic activity, resulting in delayed wound healing, as well as decreased glandular function, resulting in disturbed re-epithelialization of deep cutaneous wounds. Also seen is a reduction of melanocytes and Langerhans cells manifesting as hair graying and higher rates of infection, respectively.[2-10] Exogenously aged skin, in which environmental factors such as UV radiation act in concert with endogenous processes, shares many of the characteristics of endogenously aged skin. In addition, exogenously aged skin displays a thickened epidermis and aggregation of abnormal elastic fibers in the dermis (i.e., solar elastosis).[1]

Among the many mechanisms thought to underlie aging, glycation has emerged in recent years as one of the most widely

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studied processes. Testament to the rapidly growing attention from the scientific community, a cursory literature search will yield thousands of articles related to glycation, the majority of them published in the last decade. Glycation refers to the non-enzymatic process of proteins, lipids, or nucleic acids covalently bonding to sugar molecules, usually glucose or fructose. The lack of enzyme mediation is the key differentiator between glycation and glycosylation. Glycosylation occurs at defined sites on the target molecule and is usually critical to the target molecule's function. In contrast, glycation appears to occur at random molecular sites and generally results in the inhibition of the target molecule's ability to function. The products of glycation are called advanced glycation end products (AGEs).

Increased accumulation of AGEs was first directly correlated to the development of diabetic complications. Since then, AGEs have been implicated in a host of other pathologies, including atherosclerosis, end stage renal disease, and chronic obstructive pulmonary disease.[11] (It should be noted that AGE levels have been shown to vary by race and gender, and until larger studies are done to create ethnic- and gender-specific reference values, increased accumulation of AGEs should be defined as levels that are elevated for all demographic groups.[12]) Not coincidentally, many of the pathologies associated with AGEs, including diabetic sequelae, are closely related to senescence.

This extends to aging skin, as methods of AGE detection, such as immunostaining, have demonstrated the prevalence of glycation in aged skin. Glycation results in characteristic structural, morphological, and functional changes in the skin, a process colloquially known as "sugar sag." With glucose and fructose playing such a prominent role in the mechanism, it is not surprising that diet plays a critical role in glycation and thus aging skin.

Perhaps more surprising, studies have shown that consumption of AGEs is not only tied to the sugar content of food, but is also affected by the method of cooking. Furthermore, as the connection between diet and aging is more clearly characterized, a host of dietary compounds have surfaced as potential therapeutic candidates in the inhibition of AGE-mediated changes. In this review, we explore glycation as it pertains to skin aging and highlight evidence that demonstrates the quintessential role of diet in modifying the degree to which AGE-related processes are able to alter the largest organ of the human body.

Biochemical Processes in AGE Formation

First described over a century ago, glycation entails a series of simple and complex non-enzymatic reactions. In the key step, known as the Maillard reaction, electrophilic carbonyl groups of the sugar molecule react with free amino groups of proteins, lipids, or nucleic acids, leading to the formation of a Schiff base. This non-stable Schiff base contains a carbon-nitrogen double bond, with the nitrogen atom connected to an aryl or alkyl group. The Schiff base rapidly undergoes re-arrangement to form a more stable ketoamine, termed the Amadori product. At this juncture, the Amadori product can: (1) undergo the reverse reaction; (2) react irreversibly with lysine or arginine functional groups to produce stable AGEs in the form of protein adducts or protein cross-links; or (3) undergo further breakdown reactions, such as oxidation, dehydration, and polymerization, to give rise to numerous other AGEs.[13] AGE formation is accelerated by an increased rate of protein turnover, hyperglycemia, temperatures above 120° C (248° F), and the presence of oxygen, reactive oxygen species, or active transition metals.[14]

AGEs comprise a highly heterogenous group of molecules. The first, and perhaps most well-known, physiological AGE to be described was glycated hemoglobin (hemoglobin A1C), now widely used to measure glycemic control in diabetes. However, the most prevalent AGE in the human body, including the skin, is carboxymethyl-lysine (CML), which is formed by oxidative degeneration of Amadori products or by direct addition of glyoxal to lysine. In the skin, CML is found in the normal epidermis, aged and diabetic dermis, and photoaging-actinic elastosis.[15-17] Other AGEs detected in skin include pentosidine, glyoxal, methylglyoxal, glucosepane, fructoselysine, carboxyethyl-lysine, glyoxal-lysine dimer, and methylglyoxal-lysine dimer.[18]

AGEs and the Skin

AGEs accumulate in various tissues as a function, as well as a marker, of chronological age.[19] Proteins with slow turnover rates, such as collagen, are especially susceptible to modification by glycation. Collagen in the skin, in fact, has a half-life of approximately 15 years and thus can undergo up to a 50% increase in glycation over an individual's lifetime.[20]

Collagen is critical not only to the mechanical framework of the skin but also to several cellular processes, and is impaired by glycation in multiple ways. First, intermolecular cross-linking modifies collagen's biomechanical properties, resulting in increased stiffness and vulnerability to mechanical stimuli.[21] Second, the formation of AGEs on collagen side chains alters the protein's charge and interferes with its active sites, thereby distorting the protein's ability to interact properly with surrounding cells and matrix proteins.[22] Third, the ability to convert L-arginine to nitric oxide, a critical cofactor in the cross-linking of collagen fibers, is impaired.[23] Finally, glycated collagen is highly resistant to degradation by matrix metalloproteinases (MMPs). This further retards the process of collagen turnover and replacement with functional proteins.[24]

Other cutaneous extracellular matrix proteins are functionally affected by glycation, including elastin and fibronectin. This further compounds dermal dysfunction,[18,25] as glycation cross-linked collagen, elastin, and fibronectin cannot be repaired like their normal counterparts.

Interestingly, CML-modified elastin is mostly found in sites of solar elastosis and is nearly absent in sun-protected skin. This suggests that UV-radiation can mediate AGE formation in some capacity or, at the least, render cells more sensitive to external stimuli.[26] It is hypothesized that UV-radiation accomplishes this through the formation of superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals. This induces oxidative stress and accelerates the production of AGEs.[27] AGEs themselves are very reactive molecules and can act as electron donors in the formation of free radicals. Occurring in conjunction with the decline of the enzymatic system that eliminates free radicals during the aging process, these properties lead to a "vicious cycle" of AGE formation in the setting of UV exposure.

Formed both intracellularly and extracellularly, AGEs can also have an effect on intracellular molecular function. In the skin, the intermediate filaments of fibroblasts (vimentin) and keratinocytes (cytokeratin 10) have been shown to be susceptible to glycation modification.[28] Analogous to the diverse role of collagen in the skin, intermediate filaments are essential to both the maintenance of cytoskeletal stability and the coordination of numerous cellular functions. Fibroblasts with glycated vimentin demonstrate a reduced contractile capacity, and these modified fibroblasts are found to accumulate in skin biopsies of aged donors.[28]

In fact, general cellular function may be compromised in the presence of high concentrations of AGEs. *In vitro*, human dermal fibroblasts display higher rates of premature senescence and apoptosis, which likely explains the decreased collagen and extracellular matrix protein synthesis observed in both cell culture and aged skin biopsies.[29,30] Similarly, keratinocytes exposed to AGEs express increased levels of pro-inflammatory mediators, suffer from decreased mobility, and also undergo premature senescence in the presence of AGEs.[31]

In addition to intermediate filaments, proteasomal machinery and DNA can undergo glycation. Proteasomal machinery, which functions to remove altered intracellular proteins, decline functionally *in vitro* when treated with glyoxal.[32] Similar *in vitro* findings were observed when human epidermal keratinocytes and fibroblasts were treated with glyoxal, leading to accumulation of CML in histones, cleavage of DNA, and, ultimately, arrest of cellular growth.[33]

Beyond the modification of host molecular physicochemistry, AGEs also exert detrimental effects through the binding to specialized cellular surface receptors, called the Receptor for AGEs (RAGE). RAGE is a multiligand protein that, when activated, can trigger several cellular signaling pathways, including the mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinases (ERK), phosphatidyl-inositol-3-kinase (PI3K), and nuclear factor kappa-beta (NFκ-β) pathways.[34] These pathways are known to mediate various pathogenic mechanisms through the alteration of cell cycle regulators, gene expression, inflammation, and extracellular protein synthesis.[34] Not surprisingly, RAGE is found to be highly expressed in the skin and is present at even higher levels in both UV-exposed anatomical sites and aged skin.[35]

Combating AGE with Diet

Nearly 70 years ago, Urbach and Lentz reported that the level of sugar both in the blood and in the skin is decreased with a diet low in sugar.[36] Although its significance was not appreciated at the time, this finding demonstrated a quintessential connection between diet and skin health. We now understand that food is a source of both monosaccharides that, in high amounts, catalyze the production of AGEs in the body, and preformed AGEs.[37]

Preformed AGEs are absorbed by the gut with approximately 30% efficiency. They can then enter the circulation, where they may induce protein cross-linking, inflammation, and intracellular oxidative stress. The end result is the amplification of a similar "vicious cycle," which may be as detrimental as the consumption of excess dietary sugar.[38] Interestingly, preformed AGEs largely result from exogenous synthesis mediated by the food cooking process. Grilling, frying, deep fat frying, and roasting methods are all known to produce higher levels of AGEs in food. In contrast, methods of preparation that are water-based, such as boiling and steaming, produce a logarithmically lower amount of AGEs.[39]

A diet low in AGEs correlated with a reduction in inflammatory biomarkers (i.e., tumor necrosis factor-alpha, interleukin-6, and C-reactive protein) in diabetic human patients, as well as an improvement in wound healing and other diabetes-associated sequelae in mice.[40,41] Other authors have cited the relatively youthful appearance that is often associated with the elderly Asian population as evidence of the long-term impact of employing water-based cooking practices, which are characteristic of Asian cooking.[37]

Tight glycemic control over a 4-month period can result in a reduction of glycated collagen formation by 25%.[37,38] Consumption of a low-sugar diet prepared through water-based cooking methods would limit both the consumption of preformed exogenous AGES and endogenous production through physiological glycation. Avoiding foods that result in higher levels of AGEs, such as donuts, barbecued meats, and dark-colored soft drinks, can be an effective strategy for slowing "sugar sag."[39]

Of interest, several culinary herbs and spices are believed to be capable of inhibiting the endogenous production of AGEs (specifically fructose-induced glycation). These include cinnamon, cloves, oregano, and allspice.[42] Other dietary compounds that have been linked to inhibition of AGE formation based on *in vitro* data and preliminary animal models include ginger, garlic, α-lipoic acid, carnitine, taurine, carnosine, flavonoids (e.g., green tea catechins), benfotiamine, α-tocopherol, niacinamide, pyridoxal, sodium selenite, selenium yeast, riboflavin, zinc, and manganese.[42-44] The cosmeceutical industry has taken notice of this data, and several have recently released topical products containing carnosine and α-lipoic acid, with claims related to anti-AGE formation.[38] However, data is lacking as to whether topical administration of these compounds is as effective as dietary delivery in slowing the aging process.

Since glycation is accelerated in the presence of reactive oxygen species, antioxidants should theoretically be effective in limiting the production of new AGEs. They may also impact AGE-induced tissue damage. One intriguing study looked at the effects of the antioxidant resveratrol. Popularly known for its abundance in red wine, resveratrol is a natural phenol produced by several plants in response to injury and is found in the skin of grapes, blueberries, raspberries, and mulberries. In one study, resveratrol inhibited AGE-induced proliferation and collagen synthesis activity in vascular smooth muscle cells belonging to stroke-prone rats.[45] Another study found that it decreased the frequency of DNA breaks in methylglyoxal treated mouse oocytes. Although resveratrol does not appear to reverse the glycation process itself, these studies suggest that it can reduce AGE-induced tissue damage.[46] While these findings are promising, to our knowledge these laboratory results have not yet been demonstrated in human studies.

In one of the few human studies successfully conducted on anti-AGE therapeutics, L-carnitine supplementation for 6 months in hemodialysis patients significantly decreased levels of AGEs

in the skin.[47] L-carnitine, which is naturally abundant in meat, poultry, fish, and dairy products, is an antioxidant. Furthermore, it may function synergistically to neutralize oxidative stress when given with α-lipoic acid.[48]

It warrants mentioning that dietary caloric restriction, the most effective strategy for slowing the general aging process known to date, may function to some degree by preventing accumulation of AGEs in the human body. Caloric restriction is capable of decreasing the levels of AGEs detected in rat and mice skin collagen and has resulted in an increased lifespan in mice models.[49,50]

Conclusion: Obstacles and Future Directions

There is clearly an abundance of *in vitro* data and a handful of *in vivo* animal findings that support various options for dietary therapy directed against "sugar sag." However, studies in humans are limited by logistical, ethical, and inherent study design issues. In a stimulating commentary as part of a review article on controversies in aging and nutrition, Draelos writes about the frustrating obstacles that she encountered when she attempted to study the impact of vitamin C supplementation on skin health.[38] Examples of problems she faced included: identifying a facility that offered affordable measurements of vitamin C levels not only in the serum but also in the skin; designing an ethical study that would include a control arm requiring subjects to adhere to a diet poor in vitamin C without any supplementation; and ensuring participant compliance to the diet and supplementation protocol while also minimizing confounding factors. Most of these challenges also exist in the human studies needed to identify and/or to verify evidence-based dietary strategies in combating glycation-mediated skin aging.

Nevertheless, the role of diet in skin aging is undeniable. As our understanding of how accumulation of AGEs affects a rapidly growing number of pathologies, it is inevitable that our research methods will evolve to better address the challenges that currently seem so discouraging. For instance, a research group reported in early 2014 that they were able to successfully create a model of reconstructed skin modified by glycated collagen to identify biological modifications of both epidermal and dermal markers.[51] Perhaps the creation of an *in vitro* model that comprehensively and accurately represents aged human skin will serve as the next stepping stone in translating therapeutic findings from bench to bedside.

In the meantime, awareness of the critical impact of AGE-formation in both diabetics and non-diabetics must be extended to all patients, regardless of their current health status. That task begins with clinicians. Dietary counseling should be incorporated into our regular interactions with patients, alongside essential discussions about UV-protection and avoidance of tobacco. After all, these are the three most important known exogenous aging factors. Their common grouping is reflective of their interconnected nature and their action in concert to disturb homeostasis.

References

1. Zouboulis CC, Makrantonaki E. Clinical aspects and molecular diagnostics of skin aging. *Clin Dermatol.* 2011 Jan-Feb;29(1):3-14.
2. Elias PM, Ghadially R. The aged epidermal permeability barrier: basis for functional abnormalities. *Clin Geriatr Med.* 2002 Feb;18(1):103-20, vii.
3. Ye J, Garg A, Calhoun C, et al. Alterations in cytokine regulation in aged epidermis: implications for permeability barrier homeostasis and inflammation. I. IL-1 gene family. *Exp Dermatol.* 2002 Jun;11(3):209-16.
4. Tsutsumi M, Denda M. Paradoxical effects of beta-estradiol on epidermal permeability barrier homeostasis. *Br J Dermatol.* 2007 Oct;157(4):776-9.
5. Fimmel S, Kurfurst R, Bonte F, et al. Responsiveness to androgens and effectiveness of antisense oligonucleotides against the androgen receptor on human epidermal keratinocytes is dependent on the age of the donor and the location of cell origin. *Horm Metab Res.* 2007 Feb;39(2):157-65.
6. Makrantonaki E, Vogel K, Fimmel S, et al. Interplay of IGF-I and 17beta-estradiol at age-specific levels in human sebocytes and fibroblasts in vitro. *Exp Gerontol.* 2008 Oct;43(10):939-46.
7. Ashcroft GS, Horan MA, Ferguson MW. The effects of ageing on wound healing: immunolocalisation of growth factors and their receptors in a murine incisional model. *J Anat.* 1997 Apr;190 (Pt 3):351-65.
8. Bhushan M, Cumberbatch M, Dearman RJ, et al. Tumour necrosis factor-alpha-induced migration of human Langerhans cells: the influence of ageing. *Br J Dermatol.* 2002 Jan;146(1):32-40.
9. Zouboulis CC, Boschnakow A. Chronological ageing and photoageing of the human sebaceous gland. *Clin Exp Dermatol.* 2001 Oct;26(7):600-7.
10. Chung JH, Yano K, Lee MK, et al. Differential effects of photoaging vs intrinsic aging on the vascularization of human skin. *Arch Dermatol.* 2002 Nov;138(11):1437-42.
11. Van Puyvelde K, Mets T, Njemini R, et al. Effect of advanced glycation end product intake on inflammation and aging: a systematic review. *Nutr Rev.* 2014 Oct;72(10):638-50.
12. Mook-Kanamori MJ, Selim MM, Takiddin AH, et al. Ethnic and gender differences in advanced glycation end products measured by skin auto-fluorescence. *Dermatoendocrinol.* 2013 Apr 1;5(2):325-30.
13. Ahmed N. Advanced glycation endproducts--role in pathology of diabetic complications. *Diabetes Res Clin Pract.* 2005 Jan;67(1):3-21.
14. Thorpe SR, Baynes JW. Maillard reaction products in tissue proteins: new products and new perspectives. *Amino Acids.* 2003 Dec;25(3-4):275-81.
15. Kawabata K, Yoshikawa H, Saruwatari K, et al. The presence of N(epsilon)-(carboxymethyl) lysine in the human epidermis. *Biochim Biophys Acta.* 2011 Oct;1814(10):1246-52.
16. Dyer DG, Dunn JA, Thorpe SR, et al. Accumulation of Maillard reaction products in skin collagen in diabetes and aging. *J Clin Invest.* 1993 Jun;91(6):2463-9.
17. Jeanmaire C, Danoux L, Pauly G. Glycation during human dermal intrinsic and actinic ageing: an in vivo and in vitro model study. *Br J Dermatol.* 2001 Jul;145(1):10-8.
18. Gkogkolou P, Bohm M. Advanced glycation end products: Key players in skin aging? *Dermatoendocrinol.* 2012 Jul 1;4(3):259-70.
19. Hipkiss AR. Accumulation of altered proteins and ageing: causes and effects. *Exp Gerontol.* 2006 May;41(5):464-73.
20. Dunn JA, McCance DR, Thorpe SR, et al. Age-dependent accumulation of N epsilon-(carboxymethyl)lysine and N epsilon-(carboxymethyl) hydroxylysine in human skin collagen. *Biochemistry*. 1991 Feb 5;30(5): 1205-10.
21. Avery NC, Bailey AJ. The effects of the Maillard reaction on the physical properties and cell interactions of collagen. *Pathol Biol (Paris)*. 2006 Sep;54(7):387-95.
22. Haitoglou CS, Tsilibary EC, Brownlee M, et al. Altered cellular interactions between endothelial cells and nonenzymatically glucosylated laminin/type IV collagen. *J Biol Chem.* 1992 Jun 25;267(18):12404-7.
23. Goldin A, Beckman JA, Schmidt AM, et al. Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation.* 2006 Aug 8;114(6):597-605.
24. DeGroot J, Verzijl N, Wenting-Van Wijk MJ, et al. Age-related decrease in susceptibility of human articular cartilage to matrix metalloproteinase-mediated degradation: the role of advanced glycation end products. *Arthritis Rheum.* 2001 Nov;44(11):2562-71.
25. Nowotny K, Grune T. Degradation of oxidized and glycoxidized collagen: role of collagen cross-linking. *Arch Biochem Biophys.* 2014 Jan 15;542:56-64.
26. Yoshinaga E, Kawada A, Ono K, et al. N(varepsilon)-(carboxymethyl)lysine modification of elastin alters its biological properties: implications for the accumulation of abnormal elastic fibers in actinic elastosis. *J Invest Dermatol.* 2012 Feb;132(2):315-23.

27. Masaki H, Okano Y, Sakurai H. Generation of active oxygen species from advanced glycation end-products (AGEs) during ultraviolet light A (UVA) irradiation and a possible mechanism for cell damaging. *Biochim Biophys Acta.* 1999 Jun 28;1428(1):45-56.
28. Kueper T, Grune T, Prahl S, et al. Vimentin is the specific target in skin glycation. Structural prerequisites, functional consequences, and role in skin aging. *J Biol Chem.* 2007 Aug 10;282(32):23427-36.
29. Alikhani Z, Alikhani M, Boyd CM, et al. Advanced glycation end products enhance expression of pro-apoptotic genes and stimulate fibroblast apoptosis through cytoplasmic and mitochondrial pathways. *J Biol Chem.* 2005 Apr 1;280(13):12087-95.
30. Zhu P, Ren M, Yang C, et al. Involvement of RAGE, MAPK and NF-kappaB pathways in AGEs-induced MMP-9 activation in HaCaT keratinocytes. *Exp Dermatol.* 2012 Feb;21(2):123-9.
31. Zhu P, Yang C, Chen LH, et al. Impairment of human keratinocyte mobility and proliferation by advanced glycation end products-modified BSA. *Arch Dermatol Res.* 2011 Jul;303(5):339-50.
32. Bulteau AL, Verbeke P, Petropoulos I, et al. Proteasome inhibition in glyoxal-treated fibroblasts and resistance of glycated glucose-6-phosphate dehydrogenase to 20 S proteasome degradation in vitro. *J Biol Chem.* 2001 Dec 7;276(49):45662-8.
33. Roberts MJ, Wondrak GT, Laurean DC, et al. DNA damage by carbonyl stress in human skin cells. *Mutat Res.* 2003 Jan 28;522(1-2):45-56.
34. Bierhaus A, Humpert PM, Morcos M, et al. Understanding RAGE, the receptor for advanced glycation end products. *J Mol Med (Berl).* 2005 Nov;83(11):876-86.
35. Lohwasser C, Neureiter D, Weigle B, et al. The receptor for advanced glycation end products is highly expressed in the skin and upregulated by advanced glycation end products and tumor necrosis factor-alpha. *J Invest Dermatol.* 2006 Feb;126(2):291-9.
36. Urbach E, Lentz JW. Carbohydrate metabolism and the skin. *Arch Derm Syphilol.* 1945 Nov-Dec;52:301-16.
37. Danby FW. Nutrition and aging skin: sugar and glycation. *Clin Dermatol.* 2010 Jul-Aug;28(4):409-11.
38. Draelos ZD. Aging skin: the role of diet: facts and controversies. *Clin Dermatol.* 2013 Nov-Dec;31(6):701-6.
39. O'Brien J, Morrissey PA. Nutritional and toxicological aspects of the Maillard browning reaction in foods. *Crit Rev Food Sci Nutr.* 1989 28(3):211-48.
40. Vlassara H, Striker GE. AGE restriction in diabetes mellitus: a paradigm shift. *Nat Rev Endocrinol.* 2011 Sep;7(9):526-39.
41. Peppa M, Brem H, Ehrlich P, et al. Adverse effects of dietary glycotoxins on wound healing in genetically diabetic mice. *Diabetes.* 2003 Nov;52(11): 2805-13.
42. Dearlove RP, Greenspan P, Hartle DK, et al. Inhibition of protein glycation by extracts of culinary herbs and spices. *J Med Food.* 2008 Jun;11(2):275-81.
43. Thirunavukkarasu V, Nandhini AT, Anuradha CV. Fructose diet-induced skin collagen abnormalities are prevented by lipoic acid. *Exp Diabesity Res.* 2004 Oct-Dec;5(4):237-44.
44. Tarwadi KV, Agte VV. Effect of micronutrients on methylglyoxal-mediated in vitro glycation of albumin. *Biol Trace Elem Res.* 2011 Nov;143(2):717-25.
45. Mizutani K, Ikeda K, Yamori Y. Resveratrol inhibits AGEs-induced proliferation and collagen synthesis activity in vascular smooth muscle cells from stroke-prone spontaneously hypertensive rats. *Biochem Biophys Res Commun.* 2000 Jul 21;274(1):61-7.
46. Liu Y, He XQ, Huang X, et al. Resveratrol protects mouse oocytes from methylglyoxal-induced oxidative damage. *PLoS One.* 2013 8(10):e77960.
47. Fukami K, Yamagishi S, Sakai K, et al. Potential inhibitory effects of L-carnitine supplementation on tissue advanced glycation end products in patients with hemodialysis. *Rejuvenation Res.* 2013 Dec;16(6):460-6.
48. Hagen TM, Liu J, Lykkesfeldt J, et al. Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. *Proc Natl Acad Sci USA.* 2002 Feb 19;99(4):1870-5.
49. Cefalu WT, Bell-Farrow AD, Wang ZQ, et al. Caloric restriction decreases age-dependent accumulation of the glycoxidation products, N epsilon-(carboxymethyl)lysine and pentosidine, in rat skin collagen. *J Gerontol A Biol Sci Med Sci.* 1995 Nov;50(6):B337-41.
50. Sell DR, Kleinman NR, Monnier VM. Longitudinal determination of skin collagen glycation and glycoxidation rates predicts early death in C57BL/6NNIA mice. *FASEB J.* 2000 Jan;14(1):145-56.
51. Pageon H, Zucchi H, Rousset F, et al. Skin aging by glycation: lessons from the reconstructed skin model. *Clin Chem Lab Med.* 2014 Jan 1;52(1):169-74.

Erratum to Gooderham M, Papp K. Apremilast in the Treatment of Psoriasis and Psoriatic Arthritis. *Skin Therapy Lett.* 2015 Sep-Oct;20(5):1-6. Due to an editing error, the description of cellular events associated with inhibition of cAMP breakdown (p. 1) is inaccurate. The correct description is a follows: cAMP is a secondary messenger central for immune response regulation, and the inhibition of its breakdown leads to a cascade of cellular events resulting in a reduction of inflammatory mediators such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-23, as well as production of anti-inflammatory cytokines such as IL-10.[8,9] The authors regret the error.

Tavaborole 5% Solution: A Novel Topical Treatment for Toenail Onychomycosis

Gita Gupta MD[1,2]; Kelly A. Foley PhD[2]; Aditya K. Gupta MD, PhD, FRCP(C)[2,3]

[1]Wayne State University, Detroit, MI, USA

[2]Mediprobe Research Inc., London, ON, Canada

[3]Department of Medicine, University of Toronto, Toronto, ON, Canada

Conflicts of interest: Gita Gupta has no conflicts of interest. Aditya Gupta has been a clinical trials investigator, advisory board member, consultant, and speaker for Valeant. Aditya Gupta was involved in preclinical studies of tavaborole for Anacor Pharmaceuticals Inc. and has consulted for Anacor. Kelly Foley is an employee of Mediprobe Research Inc. which conducts clinical trials under the supervision of Aditya Gupta.

ABSTRACT

Onychomycosis is a stubborn fungal infection of the nails that can be difficult to effectively manage. One of the challenges with topical therapies is penetrating the nail plate to reach the site of infection. As the first antifungal in a boron-containing class of drugs with a novel mechanism of action, tavaborole is able to penetrate the nail plate more effectively than ciclopirox and amorolfine lacquers. In Phase II/III clinical trials, tavaborole was shown to be safe and clinically effective. Tavaborole 5% solution was approved by the US FDA for the treatment of toenail onychomycosis in July 2014 and is an important addition to the topical treatment arsenal against this stubborn infection.

Key words: clinical efficacy, dermatophyte, fungal infection, nail penetrance, nondermatophyte, onychomycosis, tavaborole, topical treatment

Introduction

Onychomycosis is a persistent fungal infection of the nails and nail bed, predominantly caused by the dermatophytes *Trichophyton rubrum* or *Trichophyton mentagrophytes*.[1] The prevalence of onychomycosis in Europe and North America ranges from 3.22-8.9%,[2,3] with recurrence and reinfection occurring in up to 25%[4]. Distal lateral subungual onychomycosis (DLSO) is the most common clinical presentation, invading the nail plate, nail bed, and hyponychium from the distal edge and lateral nail folds.[1]

Treatment for onychomycosis consists of systemic (oral) and topical medications, with or without mechanical/chemical debridement. Systemic therapy is generally more successful than topical therapy with clinical cure rates ranging from 40-80%.[5] The advantage to systemic therapy is that medication can directly reach the site of infection in the nail bed.[6] However, systemic therapy may not be feasible for those who are immunocompromised or at risk for drug-drug interactions (e.g., the elderly and/or diabetics).[7] Alternatively, other patients are uncomfortable with long-term use of oral medications. Oral antifungal medications have been associated with asymptomatic increases in liver enzymes and there is a small risk of hepatotoxic injury.[8,9] Thus, topical therapies have an important role in onychomycosis management.

The efficacy of topical therapy for onychomycosis ranges from 5.5-17.8% for complete cure and 29-55% for mycological cure.[10] The lower efficacy of topical treatments as compared to systemic therapy can be attributed to their limited ability to reach the site of infection.[11] In order for topical treatments to be effective, they need to penetrate the nail plate and down into the nail bed, and mechanical or chemical nail debridement of nails may facilitate this. The major advantage to topical therapy is that long-term use is safe, with minimal side effects.[11] Additionally, topical treatments used in combination with systemic treatment may increase clinical efficacy. Furthermore, fungal resistance to azole medications has become a concern in recent years.[12] Therefore, there is a need for new topical therapies for onychomycosis.

Tavaborole: A Novel Topical Antifungal

Tavaborole 5% solution (Kerydin®) was approved by the US FDA for treatment of onychomycosis in July 2014. Tavaborole is the first in a new class of boron atom-containing drugs, the oxaboroles. Tavaborole's mechanism of action is unique from current antifungals. Other antifungal agents act by blocking ergosterol synthesis (triazoles and terbinafine),[6] or interfering with microbial metabolism (ciclopirox).[13] Tavaborole inhibits protein synthesis, and thus fungal cell growth, by binding to leucyl-tRNA synthetase (LeuRS), an aminoacyl-tRNA synthetase (AARS).[14] AARSs are critical for correct DNA translation and contain proofreading editing sites. Tavaborole binds to the editing site of LeuRS, trapping tRNA and preventing further DNA translation and protein synthesis.[14] *In vitro* studies have shown that tavaborole can inhibit a wide range of fungal species, with minimum inhibitory concentrations (MIC) against dermatophytes, nondermatophyte molds, and yeasts (Table 1)[15] allowing for potential treatment of mixed dermatophyte-nondermatophyte/mold infections. Of note is the potential for tavaborole to act against *Fusarium* and *Malassezia* species.[15] Additionally, tavaborole's low molecular weight compared to other available topical antifungal agents appears to allow for increased nail penetrance, with increased penetrance demonstrated compared to both amorolfine and ciclopirox.[16,17]

Tavaborole's broad spectrum of antifungal activity, coupled with its ability to penetrate the nail plate, suggested that it may be an effective topical treatment for toenail onychomycosis and led to its investigation in Phase I-III clinical trials.

Clinical Efficacy

Phase I

A Phase I study assessed the efficacy of once daily tavaborole 7.5% solution for 28 days in 15 otherwise healthy patients with severe onychomycosis of both great toenails (at least 80% involvement).[18] Additionally, at least one great toenail was potassium hydroxide (KOH) positive, each great toenail had a combined thickness of the nail plate and nail bed of >3 mm, and at least six other toenails were diagnosed with onychomycosis. After 14 and 28 days of treatment, negative culture was reported for 88% (21/24) and 100% (24/24) of toenails, respectively. Clinical improvement was also observed 2-4 months following treatment, with an average clear nail growth of 1.2 mm.[18]

Phase II

Three Phase II studies have been conducted to evaluate the efficacy of a range of doses for tavaborole.[19] All of these studies enrolled adult patients (18-65 years of age) with mild to moderate onychomycosis of at least one great toenail (20-60% nail involvement) and did not allow debridement of the nails during treatment. Study 200/200A (N=187) was a double-blind, randomized, vehicle-controlled trial evaluating 2.5%, 5%, and 7.5% tavaborole solution applied to affected toenails once daily for 3 months, followed by three times weekly for 3 months.[19] The primary efficacy endpoint at 6 months was treatment success of the target toenail, defined as an Investigator Static Global Assessment (ISGA) of clear or almost clear plus negative culture or ≥2 mm of new clear nail growth plus negative culture. The rates of treatment success for all tavaborole treatments were significantly greater than vehicle control (P=0.030). While the number of patients that achieved negative culture was higher in tavaborole groups than vehicle, the differences were not statistically significant (Table 2).[19]

Studies 201 (N=89) and 203 (N=60) were open-label trials with the same primary efficacy endpoint as Study 200/200A, treatment success.[19] Patients in Study 201 applied tavaborole 5% solution (Cohort 1) or tavaborole 7.5% solution (Cohort 2) to all affected toenails once daily for 6 months. Cohort 3 applied tavaborole 5% solution once daily for 12 months. Patients in Study 203 applied tavaborole 1% once daily for 6 months or tavaborole 5% once daily for 30 days, followed by three times weekly for 5 months. Efficacy outcomes are listed in Table 2.[19] Overall, treatment with tavaborole was very promising and well tolerated, prompting larger-scale Phase III trials to be conducted. The 5% concentration of tavaborole was selected for Phase III testing.

Phase III

Two identical multi-center, randomized, double-blind, vehicle-controlled clinical trials were conducted (Study 301, N=593 and Study 302, N=601).[20,21] Patients aged 18 years and older with mycologically confirmed (positive KOH and culture)

Infectious Organisms	MIC Range (µg/ml)			
	Tavaborole	Amorolfine	Ciclopirox	Efinaconazole
Dermatophytes				
Trichophyton rubrum	1-8	0.004-0.015	0.03-1	0.001-0.015
Trichophyton mentagrophytes	2-8	0.004-0.06	0.03-0.5	0.001-0.03
Trichophyton tonsurans	2-4	0.25	≤ 0.5	0.016
Epidermophyton floccosum	≤ 0.5	0.13-0.25	0.25-0.5	≤ 0.002-0.0078
Microsporum audouinii	2	–	1	–
Microsporum canis	2	> 4	≤ 0.5	0.13-0.25
Microsporum gypseum	2	0.063-0.13	0.25-0.5	0.0039-0.016
Nondermatophyte molds				
Aspergillus fumigatus	0.25	> 4	0.25-0.5	0.031-0.5
Fusarium solani	≤ 0.5	> 4	≥ 4	0.5
Yeasts				
Candida albicans	1	≤ 0.03-8	0.06-0.5	≤ 0.0005 - >0.25
Candida glabrata	≤ 0.5	2 - >8	≤ 0.5	0.0039-0.13
Candida krusei	1	0.13-0.5	0.13-0.5	0.0078-0.063
Candida parapsilosis	≤ 0.5	0.13-4	0.13-0.5	≤ 0.002-0.016
Candida tropicalis	≤ 0.5	≤ 0.016 - >8	≤ 0.5	0.0078-0.063
Cryptococcus neoformans	0.25	≤ 0.016-0.13	≤ 0.016-0.063	0.002-0.0039
Malassezia spp.	1	–	≤ 0.5	–

Table 1. Minimum inhibitory concentration (MIC) of tavaborole and other topical treatments for toenail onychomycosis[15,22]

Study	Type	Treatment[a]	N	Assessment	Negative Culture	Treatment Success[b]
200/200A	Double-blind, Randomized	Tavaborole 7.5%	60	6 months	57/60 = 95%	19/60 = 32%
		Tavaborole 5%	31	6 months	29/31 = 94%	8/31 = 26%
		Tavaborole 2.5%	33	6 months	32/33 = 97%	9/33 = 27%
		Vehicle	63	6 months	53/63 = 84%	9/63 = 14%
201	Open	Tavaborole 7.5%	30	6 months	18/30 = 60%	16/30 = 53%
		Tavaborole 5%	30	6 months	13/30 = 43%	13/30 = 43%
		Tavaborole 5%	29	12 months	28/29 = 97%[c]	2/29 = 7%
203	Open	Tavaborole 5%	30	6 months	28/30 = 93%	15/30 = 50%
		Tavaborole 1%	30	6 months	27/30 = 90%	9/30 = 30%

Table 2. Phase II efficacy outcomes of multiple doses of tavaborole solution[19]
[a] See text for treatment regimens
[b] Investigator Static Global Assessment (ISGA) of clear or almost clear + negative culture or ≥2 mm of new clear nail growth + negative culture
[c] Measured at 6 months

onychomycosis involving 20-60% of the great toenail applied either tavaborole 5% solution or vehicle solution once daily for 48 weeks. At Week 52, complete cure (completely clear nail and mycological cure) and mycological cure (negative KOH and negative culture) were assessed (Table 3).[20,21] Treatment with tavaborole 5% solution led to a significantly greater complete cure and mycological cure rates than vehicle treatment in both clinical trials (Ps≤0.001). Additionally, the outcome of completely or almost completely clear nail (≤10% nail involvement) plus negative mycology was significantly greater with tavaborole 5% solution compared to vehicle (Study 301: 15.3% vs. 1.5%; Study 302: 17.9% vs. 3.9%, P≤0.001).[20,21]

Adverse Events

For all three Phase II studies combined, treatment-emergent adverse events (TEAEs) occurred in 177 of 366 patients.[19] There were 13 reports of serious adverse events (AEs), unrelated to treatment. A reduction in dosing frequency and/or treatment discontinuation resolved any mild to moderate application site reactions. Specifically, in Study 200/200A, four patients in the tavaborole 7.5% solution group required 'drug holidays' (discontinued treatment until persistent grade 2 stinging/burning, pruritus, or grade ≥3 irritation was resolved, then treatment resumed with reduced frequency), while no patients in the tavaborole 5% solution group required a break from treatment. Other TEAEs reported included influenza (9.0%), pharyngitis (3.8%), upper respiratory tract infection (3.6%), tinea pedis (3.8%), headache (3.6%), contact dermatitis (2.5%), onychomadesis (1.4%), and tooth extraction (0.8%).[19]

Safety data was available for 1186 participants in the Phase III clinical trials.[20] No serious AEs were considered treatment related. In both trials, discontinuation due to treatment was comparable for tavaborole 5% solution and vehicle groups. TEAEs in ≥1% of participants treated with tavaborole were limited to application site reactions (exfoliation 2.7%, erythema 1.6%, and dermatitis 1.3%), and there were few reports of TEAE's due to vehicle (exfoliation 0.3%, erythema and dermatitis 0%).[20,21] Taken together, these results demonstrate that tavaborole 5% solution is both safe and more effective than vehicle in treating toenail onychomycosis.

Discussion

Tavaborole 5% solution was approved by the US FDA in July 2014 for use as a topical treatment for onychomycosis. Phase III clinical trials demonstrated that once daily use of tavaborole 5% solution for 48 weeks produced significantly higher rates of mycological and complete cure than vehicle.[20,21] Adverse events reported from Phase II and III trials indicate that the 5% formulation of tavaborole provides optimum efficacy and safety, producing mild application site reactions in a small number of patients.[19-21] As with all topical treatments for toenail onychomycosis, treatment outcomes are, in part, reliant on patient compliance and commitment to therapy, as toenails generally require at least 10-12 months to regrow.

Study	Treatment	N	Assessment	Negative Culture	Mycological Cure[a]	Complete Cure[b]
301	Tavaborole 5%	399	Week 52	87.0%	31.1%	6.5%
	Vehicle	194	Week 52	47.9%	7.2%	0.5%
302	Tavaborole 5%	396	Week 52	85.4%	35.9%	9.1%
	Vehicle	205	Week 52	51.2%	12.2%	1.5%

Table 3. Phase III efficacy outcomes of tavaborole 5% solution[20,21]
[a] Negative KOH and negative culture
[b] Clear nail and mycological cure

Formulating an agent capable of penetrating the nail plate is one of the major challenges in developing topical treatments for onychomycosis. Tavaborole's low molecular weight and high solubility allow for greater nail penetration and subsequent delivery of medication to the nail bed. The ability of tavaborole to effectively penetrate the nail plate prevents the need for mechanical debridement that may be required with other topical treatments. Additionally, tavaborole 5% solution's broad-spectrum antifungal activity against dermatophytes, nondermatophytes, and yeasts make it a potential treatment for mixed infections. This is a relevant concern as little is known about the efficacy of current treatments for mixed infections, which may also contribute to the high recurrence rates observed in onychomycosis.

The availability of tavaborole 5% solution for the topical management of toenail onychomycosis may represent the promising start of a new line of treatments with increased nail penetrance and a novel mechanism of action against pathogenic fungi.

References

1. Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. *Clin Dermatol.* 2010 Mar 4;28(2):151-9.
2. Gupta AK, Daigle D, Foley KA. The prevalence of culture-confirmed toenail onychomycosis in at-risk patient populations. *J Eur Acad Dermatol Venereol.* 2015 Jun;29(6):1039-44.
3. Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population: a literature study. *J Eur Acad Dermatol Venereol.* 2014 Nov;28(11):1480-91.
4. Scher RK, Baran R. Onychomycosis in clinical practice: factors contributing to recurrence. *Br J Dermatol.* 2003 Sep;149 Suppl 65:5-9.
5. de Sa DC, Lamas AP, Tosti A. Oral therapy for onychomycosis: an evidence-based review. *Am J Clin Dermatol.* 2014 Feb;15(1):17-36.
6. Elewski BE. Mechanisms of action of systemic antifungal agents. *J Am Acad Dermatol.* 1993 May;28(5 Pt 1):S28-S34.
7. Baran R, Hay RJ, Garduno JI. Review of antifungal therapy, part II: treatment rationale, including specific patient populations. *J Dermatolog Treat.* 2008 19(3):168-75.
8. Garcia Rodriguez LA, Duque A, Castellsague J, et al. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol.* 1999 Dec;48(6):847-52.
9. Kao WY, Su CW, Huang YS, et al. Risk of oral antifungal agent-induced liver injury in Taiwanese. *Br J Clin Pharmacol.* 2014 Jan;77(1):180-9.
10. Gupta AK, Daigle D, Foley KA. Topical therapy for toenail onychomycosis: an evidence-based review. *Am J Clin Dermatol.* 2014 Dec;15(6):489-502.
11. Murdan S. Enhancing the nail permeability of topically applied drugs. *Expert Opin Drug Deliv.* 2008 Nov;5(11):1267-82.
12. Parker JE, Warrilow AG, Price CL, et al. Resistance to antifungals that target CYP51. *J Chem Biol.* 2014 Oct;7(4):143-61.
13. Gupta AK, Ryder JE, Baran R. The use of topical therapies to treat onychomycosis. *Dermatol Clin.* 2003 Jul;21(3):481-9.
14. Rock FL, Mao W, Yaremchuk A, et al. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site. *Science.* 2007 Jun 22;316(5832):1759-61.
15. Sanders V, Baker SJ, Alley MRK, et al. Microbiological activity of AN2690, a new antifungal agent in development for the topical treatment of onychomycosis. [Poster P1608]. Presented at the 64th Annual Meeting of the American Academy of Dermatology; March 3-7, 2006; San Francisco, CA.
16. Elewski BE, Tosti A. Tavaborole for the treatment of onychomycosis. *Expert Opin Pharmacother.* 2014 Jul;15(10):1439-48.
17. Hui X, Baker SJ, Wester RC, et al. In vitro penetration of a novel oxaborole antifungal (AN2690) into the human nail plate. *J Pharm Sci.* 2007 Oct;96(10):2622-31.
18. Beutner KR, Sanders V, Hold K, et al. An open-label, multi-dose study of the absorption and systemic pharmacokinetics of AN2690 applied as a 7.5% solution to all toenails of adult patients with moderate to severe onychomycosis. [Poster 1823]. Presented at the 65th Annual Meeting of the American Academy of Dermatology; February 2-6, 2007; Washington, DC.
19. Toledo-Bahena ME, Bucko A, Ocampo-Candiani J, et al. The efficacy and safety of tavaborole, a novel, boron-based pharmaceutical agent: phase 2 studies conducted for the topical treatment of toenail onychomycosis. *J Drugs Dermatol.* 2014 Sep;13(9):1124-32.
20. Elewski BE, Aly R, Baldwin SL, et al. Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based antifungal agent, for the treatment of toenail onychomycosis: results from 2 randomized phase-III studies. *J Am Acad Dermatol.* 2015 Jul;73(1):62-9.
21. Kerydin™ (tavaborole) topical solution, 5% [Full prescribing information]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; revised July 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204427s000lbl.pdf. Accessed September 20, 2015.
22. Jo Siu WJ, Tatsumi Y, Senda H, et al. Comparison of in vitro antifungal activities of efinaconazole and currently available antifungal agents against a variety of pathogenic fungi associated with onychomycosis. *Antimicrob Agents Chemother.* 2013 Apr;57(4):1610-6.

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Update on Drugs

Name/Company	Approval Dates/Comments
Polidocanol 1% injectable foam *Varithena®* BTG plc	Health Canada issued a Notice of Compliance in August 2015 approving Varithena® (polidocanol injectable foam) for the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein (GSV) system, above and below the knee. Varithena® is a uniform, low-nitrogen, polidocanol microfoam, dispensed from a proprietary canister device. Treatment is minimally invasive, non-surgical (no incision) and requires neither tumescent anesthesia nor sedation. Varithena® is intended for use in adults with clinically significant venous reflux as diagnosed by duplex ultrasound.
Cobimetinib + vemurafenib *Cotellic™ + Zelboraf®* Exelixis Genetech (Roche)	In August 2015, Swissmedic, the Swiss licensing and supervisory authority of Switzerland, approved cobimetinib for use in combination with vemurafenib (BRAF-inhibitor) as an oral treatment for patients with advanced melanoma. Cobimetinib is a selective inhibitor of MEK. Combined inhibition of BRAF + MEK is thought to improve outcomes in melanoma by preventing or delaying the onset of resistance seen with BRAF inhibitors alone.
Adalimumab SC injection *Humira®* AbbVie	The FDA approved this tumor necrosis factor-alpha (TNF-α) inhibitor in September 2015 for the treatment of moderate to severe hidradenitis suppurativa (HS, acne inversa). Adalimumab is the first and only FDA-approved therapy for adults with HS. The anti-inflammatory effects of TNF-α inhibition are believed to influence the pathogenic mechanisms in HS. In July, the European Commission approved Humira® for the treatment of active moderate to severe HS in adults with an inadequate response to conventional systemic HS treatment in the European Union.
Hyaluronic acid filler *Juvederm® Ultra XC* Allergan plc	The FDA granted marketing approval in October 2015 to this hyaluronic acid-based dermal filler for injection into the lips and perioral area for lip augmentation in adults >21 years of age.
Nivolumab + ipilimumab *Opdivo® + Yervoy®* Bristol-Myers Squibb Company	The FDA approved nivolumab in combination with ipilimumab in October 2015 for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma. This marks the first and only FDA approval of a novel regimen that demonstrated the potential of targeting distinct and complementary immune system pathways. Pivotal study CheckMate -069 showed significantly superior responses and progression-free survival with the nivolumab (PD-1 inhibitor) + ipilimumab (CTLA-4 inhibitor) regimen vs. ipilimumab alone. This indication received accelerated approval based on tumor response rate and durability of response.
Drug News	
Ingenol mebutate gel *Picato®* Leo Pharma	In August 2015, the FDA issued a warning about reports of severe allergic reactions and herpes zoster (shingles) associated with the use of ingenol mebutate gel. Picato® is indicated for the treatment of actinic keratosis. The agency has also received reports of cases involving severe eye injuries and skin reactions - some cases occurred when the drug was not applied according to the recommendations on the label. Consequently, the FDA is requiring changes to the label to warn about these new safety risks and to provide additional instructions on the safe and appropriate application of the product.