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MONOGRAPH

AFAMELANOTIDE

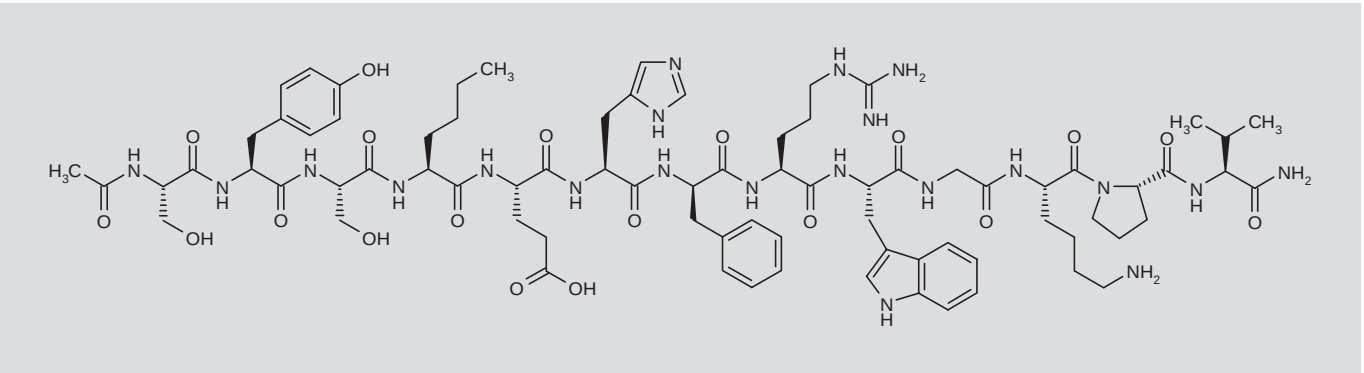
Prop INN

Melanocortin MC_1 Receptor Agonist
Photoprotective Agent

CUV-1647
ETP-1647
NDP-MSH
[Nle^4,D-Phe^7]-α-MSH
Scenesse®

Acetyl-L-seryl-L-tyrosyl-L-seryl-L-norleucyl-L-glutamyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-glycyl-L-lysyl-L-prolyl-L-valinamide

InChI: 1S/C78H111N21O19/c1-5-6-19-52(91-75(116)61(41-101)97-72(113)57(34-46-24-26-49(103)27-25-46)94-74(115)60(40-100)88-44(4)102)68(109)92-54(28-29-64(105)106)70(111)96-59(36-48-38-83-42-87-48)73(114)93-56(33-45-16-8-7-9-17-45)71(112)90-53(22-14-31-84-78(81)82)69(110)95-58(35-47-37-85-51-20-11-10-18-50(47)51)67(108)86-39-63(104)89-55(21-12-13-30-79)77(118)99-32-15-23-62(99)76(117)98-65(43(2)3)66(80)107/h7-11,16-18,20,24-27,37-38,42-43,52-62,65,85,100-101,103H,5-6,12-15,19,21-23,28-36,39-41,79H2,1-4H3,(H2,80,107)(H,83,87)(H,86,108)(H,88,102)(H,89,104)(H,90,112)(H,91,116)(H,92,109)(H,93,114)(H,94,115)(H,95,110)(H,96,111)(H,97,113)(H,98,117)(H,105,106)(H4,81,82,84)/t52-,53-,54-,55-,56+,57-,58-,59-,60-,61-,62-,65-/m0/s1



$C_{78}H_{111}N_{21}O_{19}$
Mol wt: 1646.8452
CAS: 75921-69-6
EN: 210899

SUMMARY

Artificial tanning or induction of skin pigmentation may protect individuals with light-induced skin diseases. The paracrine skin hormone α-melanocyte-stimulating hormone (MSH), acting locally at epidermal melanocytes, is a key player in the tanning response after light-induced stress. The first-in-class synthetic analogue of MSH studied in humans is afamelanotide, which has been shown to activate skin pigmentation or tanning after systemic application. Initially, afamelanotide was administered as a saline solution. Later, a slow-release formulation was used that enabled a marked reduction of the dose and side effects. It has been reported that afamelanotide reduced symptoms in different photodermatoses, including polymorphic light eruption (phase II and III), erythropoietic protoporphyria (phase II and III), phototoxicity of the skin during photodynamic therapy (phase II) and solar urticaria (phase II). However, only a few of these reports have been published. A study aimed at testing the efficacy of afamelanotide in the prevention of actinic keratosis in renal transplant patients is in progress. Reported side effects are minor, including mainly nausea and headache, and notably, no melanoma has been reported. Safety tests showed no toxic effects in mice, rats and minipigs.

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SYNTHESIS

Afamelanotide was synthesized by solid-phase synthesis using a *p*-methylbenzhydrylamine resin to which the amino acids were coupled successively as their N^{α}-Boc-protected amino acid derivatives with the reactive side-chains protected as follows: Ser as *O*-benzyl; Tyr as *O*-2,6-dichlorobenzyl; Glu as γ-benzyl ester; Lys as N^{ε}-2,4-dichlorobenzyloxycarbonyl; Arg as N^{γ}-*p*-toluenesulfonyl; His as N^{im}-*p*-toluenesulfonyl; and Trp as N^{i}-formyl. Coupling reactions were performed in excess dicyclohexylcarbodiimide and the removal of the *N*-Boc protecting groups by treatment with trifluoroacetic acid in CH_2Cl_2 and 2% anisole. After all coupling reactions, the amino terminus of the peptide resin was acetylated with *N*-acetylimidazole, the protected peptide cleaved from the resin and deprotected first by treatment with anhydrous HF containing 16% anisole and then adding 4M NaOH to pH 11.5 (1, 2).

BACKGROUND

Ultraviolet (UV) light as part of the sunlight spectrum is one of the most important environmental carcinogens (3). Besides this inherent noxious character, light of an intensity and wavelength otherwise not harmful may cause disease if it hits an abnormally reacting skin. An old phylogenic reaction of organisms to protect themselves from the noxious effects of light is to produce pigments. Such pigments, among which melanin is the most important in the animal kingdom, are able to absorb irradiating light energy and dissipate it as harmless warmth. Besides variable constitutive melanin pigmentation, animals and humans have regulatory pathways to adapt to light stress by increasing their pigment synthesis (as reviewed in 4). As will be described in more detail below, α-melanocyte-stimulating hormone (α-MSH) is a key player in this adaptive reaction.

α-MSH derives from a large gene, the pro-opiomelanocortin gene (*POMC*). The *POMC* gene product is post-translationally processed into six different peptides, including adrenocorticotropic hormone (ACTH), α-, β- and γ-MSH, β-lipoprotein and β-endorphin. ACTH and the different MSHs are also denoted as melanocortins. The tissues of major synthesis in mammals are the intermediary lobe of the pituitary gland and the skin (5). In human postnatal life, most α-MSH is synthesized and secreted in the skin, where it acts locally as a paracrine hormone (6).

The skin consists of the 10-50-μm thick epidermis and the underlying dermis. The dermis is composed of connective tissue, blood capillaries and fat cells. The epidermis consists of a keratinized stratified squamous epithelium. The most frequent cell type of the epidermis is the keratinocyte. Melanocytes are interspersed in the basal layer of keratinocytes and surrounded by about 36 keratinocytes per melanocyte (Fig. 1). The melanocytes and their neighboring keratinocytes have been called the epidermal melanin unit. The melanocytes are the only cell type of the skin capable of producing melanin pigment. Upon paracrine activation by melanocortins, the melanin pigment is synthesized and stored in small vesicular organelles called melanosomes. The melanocytes transfer the melanosomes with their dendrites to the surrounding keratinocytes. Melanin, the structure of which has not been described definitively, is a polymer of tyrosine derivatives (7, 8). There are two variants of melanin, the sulfur-containing pheomelanin, a yellow to red pigment, and the sulfur-free, brown–black eumelanin. Upon light irradiation, eumelanin produces less reactive oxygen species and is therefore more light-protective than pheomelanin (9).

The adaptive response of the skin to UV radiation damage has been discussed in excellent recent reviews (e.g., 4, 6, 10-12). Briefly, UV radiation of the skin induces damage to the DNA and other cellular structures of keratinocytes, visible as so-called sunburn cells in histology. DNA fragments with the signature of UV radiation damage, such as cyclobutane–pyrimidine dimers, lead to enhanced activity of a number of autocrine and paracrine factors, such as endothelin-1 (ET-1), basic fibroblast growth factor (bFGF) and α-MSH (10). One important factor able to sense DNA damage and mediate an adequate cellular response to this damage is the tumor suppressor p53. p53 activation promotes either apoptosis or –in less severe damage– elicits a number of repair processes, leading to long-lasting structural changes of the epidermis, i.e., increased pigmentation and thickness.

During repair, among other genes, the transcription of the *POMC* gene is activated (13). The *POMC* gene product α-MSH, synthesized and secreted by the damaged keratinocytes, binds in a paracrine fashion to a specific receptor, the melanocortin MC_1 receptor, on the neighboring melanocytes. The MC_1 receptor is a G protein-coupled receptor (14) that –after binding of an agonist– activates the enzyme adenylate cyclase via G-protein (Fig. 2). The activated adenylate cyclase forms the second messenger cAMP from ATP. The most important signaling pathway stimulates protein kinase A (PKA), which triggers the cAMP-responsive element-binding protein (CREB). This protein binds to the promoter of the microphthalmia-associated transcription factor (MITF), a nuclear transcription factor, and activates its synthesis. Phosphorylation of MITF by two other cAMP-dependent pathways leads to its activation or degradation, depending on the position of the phosphate groups (15). MITF induces, among others, the gene for tyrosinase (*TYR*), the rate-limiting enzyme of melanin formation, and the tyrosinase-related proteins TRP-1 and TRP-2. MC_1 receptor signaling results in the preferred synthesis of eumelanin rather than pheomelanin. Dendrite outgrowth, required for the distribution of newly formed melanin pigments to the surrounding keratinocytes, is induced by inhibition of

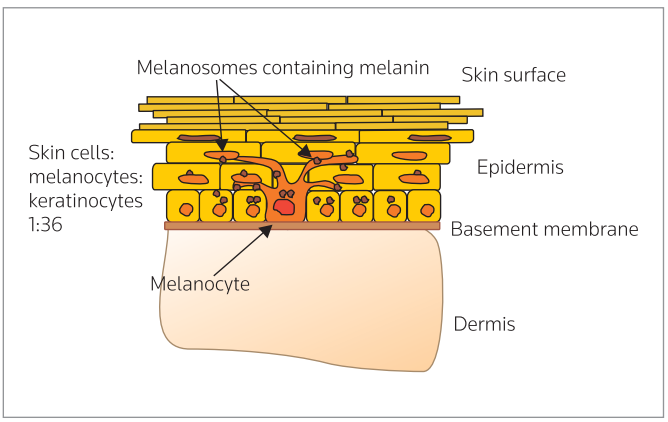

Figure 1. Schematic cross-section of the skin showing an epidermal melanin unit, a melanocyte dispensing melanosomes to the surrounding keratinocytes.

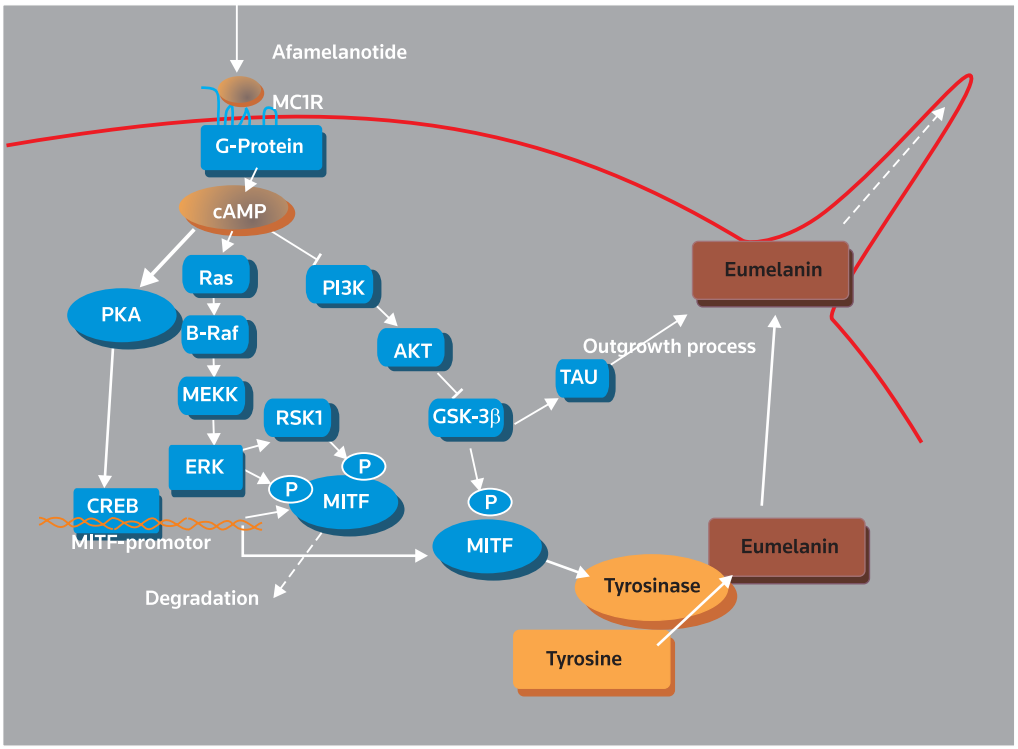

Figure 2. The melanocortin MC_1 receptor (MC1R) signaling pathways upon binding of α-MSH or its analogues (11). The main pathway is activation of protein kinase A (PKA), cAMP-responsive element-binding protein (CREB), microphthalmia-associated transcription factor (MITF) and tyrosinase. The Ras/B-Raf/MEKK/ERK pathway induces activation or degradation of MITF via phosphorylation. MITF induces the synthesis of the enzyme tyrosinase. Tyrosinase is limiting for the rate of melanin synthesis. The phosphatidylinositol 3-kinase (PI3K) pathway is inhibited by the cAMP signal. Downstream, the inhibition of glycogen synthase kinase 3-β (GSK-3β) by Akt is relieved, which enhances the outgrowth of dendrites and activation of MITF by phosphorylation. Adapted from M. Khaled, L. Larribere, K. Bille, E. Aberdan, J.-P. Ortonne, R. Ballotti, C. Bertolotto. *Glycogen synthase kinase 3β is activated by cAMP and plays an active role in the regulation of melanogenesis.* J Biol Chem 2002, 277(37): 33690-7, 2010, © 2010 The American Society for Biochemistry and Molecular Biology.

phosphatidylinositol 3-kinase (PI3K)-depdenent signaling (16). Thus, MC_1 receptor signaling controls both melanin synthesis and melanin distribution.

After UV radiation-induced cellular damage, α-MSH and its analogues enhance repair processes, specifically the excision of the DNA photoproducts cyclobutane–pyrimidine dimers, and inhibit the intrinsic apoptosis pathway (17). This effect is apparently not dependent on melanin formation and depends on an induced rather than inhibited PI3K pathway (18). In this context, it is also of importance that α-MSH has indirect antioxidant effects on epidermal cells, e.g., by inducing nuclear factor erythroid 2-related factor 2-dependent antioxidant enzymes (19) or catalase (17).

The skin is constitutively protected against UV radiation by at least two different substances: in the low UV region by urocanic acid and over the whole UV and visible light spectrum by the melanins. The melanosomes not only absorb irradiating light, but also reflect it (20). As the melanosomes accumulate like a cap above the cell nucleus, they specifically protect the most UV-sensitive cellular component, the DNA, from irradiation damage.

In the central nervous system (CNS), α-MSH and its analogues induce satiety and enhance sexual function upon their binding to another receptor type, the melanocortin MC_4 receptor (21, 22). Apparently, the linear structure prevents afamelanotide from crossing the blood–brain barrier after systemic application (23), in contrast to the closely related but cyclic bremelanotide (PT-141). Therefore, afamelanotide has no CNS effects and consequently the risk of side effects is reduced. Many additional physiological or pharmacological activities have been ascribed to the melanocortins, including reduction of inflammation and immunomodulation (14, 24, 25).

A therapeutically induced augmentation of skin melanin by α-MSH analogues has been considered an option to prevent symptoms in light-induced skin diseases. Potential candidates are skin diseases mitigated by high skin melanin content either as a constitutive factor or after induction by phototherapy. Afamelanotide is the first-in-class analogue of the natural hormone α-MSH. Compared to α-MSH, afamelanotide is substituted at two amino acid positions, at position 4 by norleucine instead of methionine and at position 7 by *d*-phenylalanine instead of *l*-phenylalanine. These changes enhance the biological activity compared to α-MSH.

The effects of afamelanotide are being studied in different types of light-provoked skin diseases: 1) in dermatoses in which irradiating light activates an accumulated pathological photosensitizer and induces a phototoxic skin reaction, such as erythropoietic protoporphyria (EPP) and photodynamic therapy (PDT); 2) in those photodermatoses in which photosensitivity is elicited by photoactivation of an unknown chromophore (solar urticaria, SU) or of an unknown allergen, resulting in an altered immunological reaction (polymorphic light eruption, PLE); and 3) in chronically altered skin due to UV radiation-induced DNA damage that results in an increased mutation rate and a corresponding risk of skin cancer. In detail, the efficacy of afamelanotide has been studied in the following disorders.

Diseases with phototoxicity

EPP is an inborn error of heme metabolism with an estimated frequency in Caucasians of about 1:150,000 (26, 27). An enzymatic deficiency of the last enzyme of heme biosynthesis, ferrochelatase, results in the accumulation of its substrate, protoporphyrin. Protoporphyrin is a strong photosensitizer, activated by light in the visible blue wavelength range. Persons affected by EPP react with painful phototoxicity in skin areas exposed to sunlight for only a few minutes. If patients cannot avoid further sun exposure, long-lasting, incapacitating pain results. Objectively, the skin may look normal or slightly erythematic, but in the severest attacks, edema, petechiae, skin lesions and general malaise appear. The light-induced pain in EPP is so intense that opioid-like substances are required for its alleviation. Neither steroids nor antihistaminics have a substantial effect. The first manifestation occurs early in childhood and symptoms remain during the subject's entire life. Strong limitations in both social and professional activities result. β-Carotene and many other substances have been applied with minimal or no efficacy (28).

Interestingly, black subjects of sub-Saharan origin have never been reported to suffer from EPP except for two only minimally documented cases. The lack of studies on EPP in black-skinned individuals is probably due to the low number of affected individuals. One possible explanation is that black persons are protected by their constitutively high skin eumelanin. An alternative reason is a genetic factor that reduces their risk of suffering from EPP (29).

Photodynamic therapy (PDT) can be considered as iatrogenic EPP. In PDT, highly fluorescing compounds, such as protoporphyrin or porphyrin derivatives, that preferably locate to precancerous or cancer cells are applied to patients. Abnormal cells are identified by their specific pink porphyrin fluorescence and can be specifically destroyed by irradiation with high-energy artificial light. PDT is especially used in cancers on natural surfaces of the body, such as on the skin or in the gastrointestinal tract, as these areas are accessible to high-energy light. Owing to the selective accumulation of the porphyrins in abnormal cells, normal tissue is spared from destruction, a major advantage of PDT. With a delay compared to cancer cells, normal skin cells also accumulate the photosensitizer, resulting in severe phototoxicity similar to EPP (30). Such light-sensitive PDT patients may suffer from severe skin burns if they do not protect themselves carefully from sunlight until protoporphyrin is degraded, which requires days to weeks, depending on the photosensitizer used.

Diseases with photosensitivity

PLE is the most common photodermatosis (31), characterized by itchy papules and small vesicles elicited by sunlight irradiation. Typically, this papulovesicular rash occurs on skin areas normally covered during the winter. The pathomechanism of PLE remains unknown, but is most likely due to a delayed-type hypersensitivity reaction elicited by light-induced conversion of an unknown precursor to an antigen. The first manifestation occurs mainly in the second and third decades of life. Female individuals are more often afflicted than males, and fair-skinned subjects more frequently than dark-skinned persons. Typically, its symptoms are strongest in spring and early summer, and gradually disappear during the late summer, autumn and winter. As a first-line therapy, topically or systemically applied steroids are administered, but their long-term application is accompanied by adverse effects such as skin atrophy or osteoporosis. Moderation of sun exposure, high-factor broad-spectrum sunscreens, PUVA (psoralen + UVA) or UVB narrow-band phototherapy are used as preventive measures. In exceptionally severe cases, immunosuppressive therapy may be indicated.

SU is a very rare, probably acquired disease (32). Affected persons react to sunlight with urticaria, itching and burning. Pathognomonic wheals and flares develop within 5-10 min of exposure to light of a wavelength between 300 and 500 nm, infrequently up to 700 nm or to the infrared region. In rare cases, it progresses to an acute anaphylactoid reaction with breathing difficulties, fainting or shock. The first manifestation usually occurs in young adulthood, and less frequently in childhood or late in life. Exposure to light of another wavelength than the provocative one as given by phototherapy can induce tolerance. The mechanism of action of this therapeutically used option has not been elucidated, but induction of melanin synthesis is one possibility. Sunscreens, oral antihistamines, systemic immunosuppressants, plasmapheresis or a combination of these modalities have been used as alternative therapeutics, with little efficacy. The management of solar urticaria remains problematic for many patients.

Diseases characterized by light-induced malignant skin alterations

Actinic keratosis is an early in situ squamous cell carcinoma of the skin with a 0.25-20% risk per year to progress to invasive squamous cell carcinoma (33). The risk of actinic keratosis or squamous cell carcinoma correlates with the life-long cumulative dose of UV radiation on the skin. High-risk populations include fair-skinned persons, the elderly, persons with a history of sunbed use, and subjects receiving PUVA therapy or immunosuppressants. In contrast, dark skin pigmentation seems to be protective (34, 35). Actinic keratosis has been described as a disease not limited to single clinically apparent lesions. Rather, it includes an enlarged skin area that looks clinically normal but harbors cells with preneoplastic UV radiation-induced mutations, a phenomenon called field cancerization. Therapies aimed to remove the clinically apparent lesions are PDT, topical 5-fluorouracil, cryotherapy, topical diclofenac and topical imiquimod cream. Imiquimod also reduces the long-term recurrence rate (36).

As stated before, all the diseases described above are apparently mitigated by either constitutional or exogenously induced intense

skin pigmentation and are therefore potentially amenable to treatment by iatrogenic melanization of the skin.

PRECLINICAL PHARMACOLOGY

In the 1960s α-MSH was detected as a hormone inducing skin pigmentation in the frog and later in humans (37). The analogue afamelanotide was first synthesized in 1980. Afamelanotide was not only more potent, but its activity lasted longer in biological systems than the native hormone (1). Today it is considered to be the most potent α-MSH analogue ever synthesized (38). A tripeptide sequence, Phe-Arg-Trp, has been identified as a minimal message sequence (39). To exert its function, α-MSH or its analogues bind to specific receptors, called melanocortin receptors. There are five different melanocortin receptors: MC_1, MC_2, MC_3, MC_4 and MC_5. Skin cells carry the MC_1 receptor on their surface, whereas, as stated above, the activity in the CNS is mediated by the MC_4 receptor. The adrenal cells carry the MC_2 receptor, which has high specificity for ACTH. α-MSH and its analogue afamelanotide bind specifically to MC_1, MC_3, MC_4 and MC_5 receptors. The K_i values for afamelanotide in competition with [^{125}I]-afamelanotide are 0.085, 0.4, 3.8 and 5.1 nmol/L, respectively (40).

The *MC1R* gene has many polymorphisms in the Caucasian population, leading to low activity variants. Most of these polymorphisms are related to variations in skin and hair pigmentation, e.g., red hair and white skin unable to tan, as well as to the susceptibility to melanoma and skin cancer (41-45). In contrast to the natural hormone α-MSH, afamelanotide's binding capacity and its potency to generate cAMP in vitro are influenced little by changes of single amino acids in the binding domains of the MC_1 receptor (46, 47). This finding is likely to explain why, after afamelanotide application, humans with allelic *MC1R* variants increase their tan to a greater extent than those without these variants (48).

PHARMACOKINETICS AND METABOLISM

Initially, afamelanotide was applied subcutaneously (s.c.) in a saline solution, as it does not penetrate the epidermis in a topically applied formulation. In saline and at a high dose, afamelanotide had a significant number of side effects, especially nausea and vomiting, flushing of the head and neck, and headaches. The half-life of afamelanotide applied s.c. in saline solution was 0.07-0.79 h in the absorption phase and 0.8-1.7 h in the β-phase (49). The clearance was 0.12-0.19 L/kg/h. Subcutaneously and orally applied afamelanotide was 100% and 0% bioavailable, respectively. The degradation is thought to be catalyzed by nonspecific proteases. Despite its short half-life, afamelanotide-induced skin pigmentation lasts at least 2 months (38).

A sustained- and controlled-release formulation improved efficacy and markedly reduced adverse effects. In saline, maximal effects on melanin production were found at 0.16 mg/kg/day during 10 days per month, corresponding to 224 mg per 2 months in persons of 70 kg body weight. As a controlled-release formulation, maximal efficacy with about the same increase in melanin density as the saline solution was obtained with 16 mg once every 2 months, but pharmacokinetics of the controlled-release implant have not been published. Even if the dose for maximal efficacy on melanin induction differs by a factor of 14 between the saline solution and the controlled-release formulation, the difference in the AUC may be smaller between the two formulations. Pigmentation as a synergistic local UV response is enhanced in sun-exposed compared to sunlight-shielded skin areas (38, 50). After repeated doses, sun-shielded skin areas may increase their pigmentation more than sun-exposed areas (50). The photoprotective effect of afamelanotide-induced pigmentation was proven by a 59% reduction of thymine dimer formation and a > 50% reduction of apoptotic sunburn cells in the epidermis after controlled UV exposure (51).

SAFETY

Data on preclinical toxicology have been published by Hadley and Dorr (38). The species tested were mice, rats and minipigs. Doses up to 2 mg/kg/day during 12 weeks in mice, 0.6 mg/kg/day during 30 days in rats and 0.16 mg/kg/day during 30 days in pigs caused no signs of toxicity other than a small increase in lactate dehydrogenase in rats. Intrauterine application during pregnancy days 5-19 in rats did not adversely affect the organogenesis of the fetuses.

The question frequently arises as to whether afamelanotide may induce malignant transformation of melanocytes. In our opinion there is sufficient evidence that α-MSH and its analogues do not cause or are not associated with malignant transformation or uncontrolled cellular proliferation of melanocytes. Increased MC_1 receptor signaling in melanocytes is associated with increased pigmentation, a differentiation function. Normal melanocyte stem cells and melanoblasts do not express the MC_1 receptor and so are not inappropriately activated in response to UV radiation, whereas differentiated melanocytes do express the receptor (52). Human melanoma tumors comprise a mixed population of cells (53-55), only some of which are likely to express the MC_1 receptor. The techniques used so far to examine expression of the MC_1 receptor in melanoma cells do not discriminate between subpopulations of different levels of differentiation. Given the parallels with normal melanocytes, it is plausible that melanoma stem cells are unlikely to express the receptor and the more differentiated the melanoma cell, the more the receptor is expressed. Again, like normal melanocytes, activation of the receptor is likely to promote differentiation (56). Increased α-MSH expression might be associated with a subset of melanoma tumors, since some of the tumor cells may be producing MSH (57, 58). However, this does not indicate that increased α-MSH is causative for melanoma induction, just as increased melanin associated with melanoma does not cause melanoma.

Additionally, melanomas are characterized by genomic damage and derailment of cellular processes that either lead to activation of survival signaling pathways or to suppression of tumor suppressive pathways. One frequently observed activating mutation, BRAFV600E, is present also in most benign nevi and thus is not sufficient to induce malignant transformation. The melanocytes of the nevi carrying the BRAF mutation are physiologically exposed to α-MSH during natural tanning processes. In case α-MSH would cause malignant transformation of these mutated melanocytes, the transition of benign to malignant melanoma would be much more frequent than observed taking the number of nevi present in fair-skinned people and the incidence of melanoma of about 2-10/100,000 into account (59, 60).

Finally, enhanced proliferation of melanocytes in culture will only be observed in the presence of other mitogens in addition to α-MSH (61). In a murine model of melanoma cell growth, application of afamelanotide neither increased the size of the primary tumor nor affected the occurrence of lung metastasis or the survival time (62).

Consumption of internet-based illegally distributed MSH agonists is widespread in some specific subcultures, especially in bodybuilders (63). Health authorities and researchers have issued warnings against their use (64-66). Four reports of adverse effects of illegal preparations have been published (65-68). The first published report described rapid changes in pigmentation and the appearance of pre-existing nevi, while the other two reported eruptive atypical nevi, both events occurring within a few days after the start of the illegal application. The fourth one described the coincidence of a 4-week course of an illegial NDP-α-MSH preparation with a growing pigmented lesion later classified as melanoma by histology. Illegally prepared and distributed drug substances contain major contaminants. The toxicity of these preparations cannot be extrapolated to a medication prepared under GMP conditions.

CLINICAL STUDIES

Initially, afamelanotide was applied daily as a saline solution. First, easily tanning (skin type III and IV) and poorly tanning Caucasians (skin type I and II) were tested. Both groups developed increased melanin content in their skin (69). Later it was found that volunteers of skin type I and II increased their melanin content to a greater extent than those of skin type III and IV (51).

A slow- and controlled-release implant formulation showed improved efficacy for tanning and less adverse effects compared to saline preparations. Dose increase studies between 5 and 40 mg per implant demonstrated that melanin pigmentation induction was maximal after 16 mg (38).

In PLE patients, afamelanotide significantly reduced the use of (systemic) steroids compared to placebo, there was a strong trend for a reduction in the frequency of PLE symptoms and melanin density was significantly induced according to the trial sponsor, but no peer-reviewed publication is yet available (70).

In an open-label study of 4 months' duration, a small group of 5 EPP patients were treated with two 20-mg slow-release afamelanotide implants 60 days apart. Their pain tolerance to provocation by artificial light and their skin pigmentation increased by a factor of 11 and 1.3 ($P = 0.004$ and $P = 0.007$), respectively (50, 71). The maximum duration of sunlight tolerated by the 5 patients within 1 day was 360, 210, 180, 120 and 30 min, respectively, representing 1,200%, 350%, 1,800%, 2,400% and 75%, respectively, of the baseline time.

Wheal size and wheal formation at 30 and 60 days were significantly reduced in SU patients ($P < 0.003$). More importantly, the minimal urticarial dose, a measure for UV and sunlight tolerance, was significantly increased in all patients (72).

A small double-blind study included 16 PDT patients. Those treated with afamelanotide reported a better quality of life than those on placebo (73).

An ongoing phase II study is examining the potential of afamelanotide for preventing actinic or squamous cell carcinoma in kidney transplant patients.

A multicenter, double-blind, placebo-controlled study of 1 year duration in about 100 EPP patients was performed in Europe and Australia. Preliminary data from the Swiss cohort showed a significant reduction in the intensity of phototoxic episodes, and increased sunlight exposure during afamelanotide treatment compared to the placebo phase (74). Preliminary data on the first 4 study months of the entire cohort confirmed a significant reduction in the intensity of phototoxic episodes (75).

Preliminary results have been announced by Clinuvel from a double-blind, placebo-controlled trial in PLE patients, with a trend towards a reduction in the Physicians' Global Severity Index at study day 150 ($P = 0.077$), but not at day 120 ($P = 0.448$) (76). A follow-up trial will be conducted this year.

CONCLUSIONS

Despite the fact that efficacy data on afamelanotide published in peer-reviewed journals are still limited, the available information leads us to expect that afamelanotide will provide an effective and safe therapeutic tool in a number of light-related skin diseases in the future. This first-in-class compound will likely be followed by a number of analogues with additional potential. An outlook on other physiological and pharmacological characteristics described for this class of substances, including modulation of immunological skin reactions, suppression of reperfusion injury and improvement of sexual function, to name just a few, raises the expectation of a broad clinical application for this drug class in the future.

SOURCE

Clinuvel Pharmaceuticals, Ltd. (AU).

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DISCLOSURES

The author states no conflicts of interest.

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