

Afamelanotide in protoporphyria and other skin diseases: a review

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Abstract

Afamelanotide is a synthetic alpha melanocyte stimulating hormone presenting a higher activity than natural hormones. Its main properties are related to the enhanced production of eumelanin by agonistically binding to the melanocortin-1 receptor. Since 2016 afamelanotide has been especially applied to treat cases of erythropoietic porphyria (EPP), where painful photosensitivity has been observed since early childhood. The positive effect of afamelanotide in EPP administered subcutaneously improved tolerance to artificial white light and increased pain-free time spent in direct sunlight. In this review we summarize the possible use of afamelanotide in dermatology, with special emphasis on EPP and encourage including afamelanotide as a treatment option in patient care.

Key words: afamelanotide, protoporphyria, erythropoietic porphyria.

Physiological mechanism of α -melanocyte-stimulating hormone (α -MSH) and its agonist

The natural α -MSH belongs to the melanocortin family and is produced by the pituitary gland as the product of proopiomelanocortin (POMC) post-translational processing. It exhibits vast amounts of activities within the skin including anti-inflammatory and immunosuppressive effects. As an endogenous peptide (compound of 13 amino acids) with paracrine and autocrine effects on melanocytes, it may stimulate melanogenesis via the melanocortin-1 receptor (MCR1) as well as tyrosinase activation, leading to skin-darkening by eumelanin synthesis [1, 2]. This brown-black pigment presents a photoprotective effect, while pheomelanin – a yellow-red pigment – contributes to UV-skin damage by generation of free radicals. The predominance of pheomelanin in individuals who present loss-of-function variants of MCR1 leads to a high risk of melanoma and skin cancers [3–5]. The expression of MCR1 is observed not only on melanocytes but also on fibroblasts, keratinocytes and endothelial cells and results in many biological protective effects including antioxidant activities, DNA repair mechanisms and immunomodulatory effect by stimulation of interleukin (IL)-10 [6].

Afamelanotide was developed in 1980 at the University of Arizona as the first synthetic α -MSH analogue, al-

though it acts in the same way as endogenous MSH and MCR1 in eumelanogenesis [7]. Afamelanotide is a structural analogue (synthetic tridecapeptide) of α -MSH. The molecule is a melanocortin receptor agonist and binds predominantly to the melanocortin-1 receptor (MC1R), however its binding lasts longer than that of α -MSH. Afamelanotide is therefore resistant to breakup by proteolytic enzymes within a short time. It is hydrolyzed immediately, but its metabolites' pharmacokinetics and pharmacodynamics have not yet been fully investigated. It is suspected that afamelanotide mimics endogenous compound's pharmacological activity by activating the synthesis of eumelanin mediated by the MC1R receptor. Eumelanin on the other hand contributes to photoprotection by acting towards strong broadband absorption of UV and visible light, presenting antioxidant activity through scavenging of free radicals and also inactivating superoxide anion and increased availability of superoxide dismutase to reduce oxidative stress. Afamelanotide differs from the natural hormones in its stereo-chemical structure (substitution of additional amino acids at position 4 and 7), which makes it more potent having a longer biological activity. Its activity, stability, and capacity to stimulate tyrosinase activity was found to be up to 1,000 times higher on animal models. Furthermore, afamelanotide works independently of UV stimulation, although

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UV exposure amplifies melanogenesis and increases the epidermal proliferation longer than after single sun exposure. What is more, *in vitro* and *in vivo* studies suggested that afamelanotide enhanced the DNA repair process after UV damage on keratinocytes [7–11]. Clinical studies were performed starting in patients with erythropoietic protoporphyria (EPP).

The approval of afamelanotide by the European Medicines Agency for the prevention of phototoxicity in adult patients with EPP was issued in December 2014. Since then, the promising therapeutic effects of this medication have been presented, also in other skin diseases where photosensitivity reaction is observed [10–13]. The aim of the presented study was to show possible use of afamelanotide in dermatology with particular focus on EPP in addition to sharing the experience on the treatment. The obtained results show safety of afamelanotide. Until now, no serious drug-related adverse effects have been reported, however such problems as nausea, headache, and skin pigmentation (freckles, skin darkening) may appear.

Skin diseases with the use of afamelanotide

Erythropoietic protoporphyria (EPP)

EPP (OMIM 177000) belongs to the rare autosomal recessive inherited disorders with the defect in heme biosynthesis. Its prevalence ranges between 1 : 75,000 and 1 : 180,000 in Europe [14–16]. The milder variant of EPP, related to the partial deficiency of ferrochelatase is observed in the Japanese population with increased frequency (43% of the Japanese population). In > 90% of cases, EPP is caused by the mutations in the FECH gene, which decreases the activity of ferrochelatase. This enzyme is responsible for incorporating ferrous iron into the tetrapyrrole ring during the conversion of protoporphyrin IX to heme [16]. Other rare causes of EPP are X-linked (XLP, OMIM 300752), they account for 2–10% of cases resulting from an overactive enzyme: erythroid-specific aminolevulinic acid synthase 2 (ALAS2) [17].

The clinical manifestations of EPP results from accumulation of protoporphyrin IX which is the photosensitizing agent that can be activated by the blue spectrum (400–410 nm) of visible light [16]. Short-time exposure to light causes severe pain (neuropathic pain) in children, which usually occurs 1–20 min after direct exposure to the sun and may last several days and be unresponsive to analgesics. The skin may become erythematous and oedematous, with the presence of petechiae and erosions [16, 18, 19]. Quality of life in patients suffering from EPP is severely affected since early childhood due to their light-avoiding behaviour and limitations in social interactions [20]. The other affected organ is the liver, which is involved in 5–20% of cases and may manifest in cholestatic hepatitis that can progress to liver failure requiring transplantation [16, 20].

Before the era of afamelanotide, light avoidance, wearing protective clothes and application of yellow films on windows (to block blue light) were the main methods in prevention of phototoxicity in EPP. The quality of life in those patients was extremely decreased followed by social withdrawal. The several methods to reduce this effect were discussed in the literature and publications, however a systematic review of more than 20 studies showed little to no benefit [21]. Use of sunscreen products is ineffective as they only block UVA and UVB wavelengths. However, the inorganic sunscreens were suggested to reduce the penetration of light into the dermis [22]. To prevent blue light from penetrating the skin and activating protoporphyrin IX, the β -carotene was previously studied, which leads to orange skin pigmentation. However, there are only small and limited numbers of trials, with one of them randomized from 1977, which shows inconclusive effects [23–26].

Another potentially effective form of therapy is narrowband ultraviolet B phototherapy (NBUVB), widely used as a prophylactic measure for various photodermatoses. Also some of the EPP patients reported an increase in duration of tolerance to sunlight up to more than an hour after NBUVB compared with only a few minutes before therapy. A suspected mechanism of tolerance induction could be associated with physical photoadaptation, as well as effect on mast cells, also possibly contributing to the patient's benefit. This type of treatment is however limited due to the increased risk of DNA mutations and diversified patient response [27, 28].

There was no proven effect of anti-free-radical options, including cysteine, vitamin C and dihydroxyacetone in EPP [21]. Blood transfusions as well as exchange transfusions were found to be an indispensable treatment in EPP-related acute cholestatic hepatitis. Allogeneic bone marrow transplantation, mostly combined with liver transplantation is proposed as treatment to severely affected patients with liver damage [29, 30].

Introduction of afamelanotide in EPP therapy provided photoprotection by increasing eumelanin density [16, 21, 31]. Its first positive effects in EPP were observed in 2006, when slow release formulated afamelanotide 20 mg administered subcutaneously given twice at an interval of 60 days in 5 patients improved tolerance to artificial white light [16]. In this photo-provocation study, intolerable pain on the dorsum of the hand following exposure of UV-light was set as the termination criteria (primary endpoint). The results showed an increase of 11 times longer time to response [16, 32]. A phase III, randomized placebo-controlled double-blinded crossover study (CUV017) included 100 EPP patients from Europe. In 2009, a pharmaceutical company announced preliminary results from its study showing prolonged spontaneous exposure to sunlight in EPP patients and their reduced pain [16]. In 2015, Langendonk *et al.* presented the results of a trial which included 168 patients in two study groups

(74 patients in the European Union trial and 94 patients in the US trial) [33]. Patients received a subcutaneous implant containing either afamelanotide or placebo every 60 days (a total of five implants in the European Union study and three in the US study). In both study groups, the quality of life improved and pain-free time after administration of afamelanotide was significantly longer than in the placebo groups (6 months longer in the US group and 9 months longer in European patients). What is more, the number of phototoxic reactions was lower in the afamelanotide group and recovery time was significantly faster in patients from Europe (receiving afamelanotide longer) [33].

Observational studies that followed showed safety of afamelanotide treatment and improvement in quality of life [34, 35]. In one report, the tested termination criterion (endpoint) was the phototoxic burn protection factor, which is the maximum time the patients are able to expose themselves to sunlight without experiencing a phototoxic reaction. During afamelanotide treatment in EPP this factor increases, with a decrease in pain severity [34].

In all studies, afamelanotide was well tolerated without severe side effects. However, patients complained

about adverse effects such as headaches, nausea, nasopharyngitis or back pain as well as fatigue [33–35]. Even 89% of patients experienced self-limiting side effects, with an average duration of one to two days, which are usually observed within hours and up to 1 day after implantation. The most prominent effect of afamelanotide is skin hyperpigmentation which is not considered to be a side effect [16, 36].

Currently, afamelanotide is the only licensed systemic drug for the treatment of EPP patients worldwide. According to the EMA, it is recommended for adult patients at a dose of 16 mg subcutaneously (implant), four times per year, with at least 60 days between implantations. It is worth emphasizing that the prescription and use of the reimbursed drug is limited to accredited, specialized and experienced porphyria centres (Figure 1). Such centres are localized in Switzerland, the Netherlands, Germany, whereas in Belgium, Austria and Italy, reimbursement of afamelanotide is based on a case-by-case decision. In 2019, the Food and Drug Administration (FDA) approved EPP in the USA and in 2020 EPP was approved in Australia. A new promising molecule MT-7117 (dersimelagon) is under investigation as an oral alternative to afamelanotide for adults and adolescents [37].



Figure 1. Photographs of clinical symptoms off EPP and Scenesse® implantation. Upper panel: acute and chronic skin lesions in two patients with EPP after sun exposure. Lower panel: Scenesse® implant (approximately 1.7 cm in length and 1.5 mm in diameter) before and during the subcutaneous implantation

Polymorphic light eruption

Polymorphic light eruption (PLE) is the most prevalent idiopathic photodermatosis, which is probably mediated immunologically, as a fourth type of the hypersensitivity reaction to an unknown antigen expressed after sun exposure. UVA (320–400 nm) is regarded to be the main triggering factor [38, 39]. However, a possible genetic predisposition of PLE was suggested due to its prevalence in North and Latin American Indian populations as well as among the Finnish population. It usually affects women's skin in sun exposed areas during annual irradiation, especially in spring or summertime. Skin lesions may have a wide range of manifestations, including erythema, papules, papulovesicles or even blisters. Some lesions may mimic erythema multiforme or purpura. They are typically presented within hours or days after exposure and can be associated with an itching sensation. As a prevention, sun avoidance, use of broad-spectrum sunscreens and antioxidants, together with symptomatically applied topical glucocorticosteroids, is usually recommended [38, 39]. There is good evidence that phototherapy and photohardening are beneficial in the management of these patients. Prophylactic desensitization with the use of small doses of UV irradiation (phototherapy with either low-dose psoralen ultraviolet A (PUVA), broadband ultraviolet B (BB-UVB) or narrowband UVB (NB-UVB)) should start 1 month before the expected onset of the skin lesions [10, 40]. A possible new agent in PLE treatment is afamelanotide, which causes photoprotection via hyperpigmentation, similar to adaptation induced by phototherapy. Additionally, other biological effects of afamelanotide like antioxidant activities, DNA repairment and immunomodulatory effect are beneficial in this respect. In 2010, a phase III, randomised, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of subcutaneous 16 mg of afamelanotide in 15 PLE patients was started (NCT04704713). Another trial was conducted on 18 PLE patients and showed a tendency in reduction of the severity of symptoms in comparison to the placebo group (NCT00472901). However, as we know, the results have not been published yet.

Solar urticaria

Solar urticaria is another photodermatosis, where afamelanotide may be of use. The trigger or causes are still discussed in this orphan subgroup of chronic inducible urticaria. It is considered to be an immunologically mediated activation of cutaneous mast cells triggered by specific wavelengths of UV radiation. After several minutes of sun exposure (usually 5–15 min) patients experience a rapid development of pruritus, erythema and wheals. However, 10% of patients with severe solar urticaria may also suffer from systemic symptoms, for example nausea and headaches, although a few isolated cases of syncope or anaphylaxis have also been documented. The

main treatment options in solar urticaria include sunlight avoidance, use of sunscreens and antihistamines. In severe cases, omalizumab or ligelizumab (anti-IgE monoclonal antibody) was proposed [41, 42]. Omalizumab is licensed for chronic spontaneous urticaria and could be used as an off-label treatment for patients with severe solar urticaria. One study demonstrated the successful use of afamelanotide in 5 patients with solar urticaria [43]. A 16 mg subcutaneous afamelanotide implant was administered during wintertime with melanin density assessed spectrophotometrically from day 0 to day 60. The authors showed quantitatively that this agent is able to convincingly reduce the symptoms of solar urticarial. They also presented the possibility of photoprotection at wavelengths within the range of 300–600 nm and significant reduction in the wheal area accompanying significant increases in melanisation at exposed and unexposed skin sites [10, 43].

Vitiligo

Vitiligo is another type of skin disease with photosensitivity where trials with the use of afamelanotide were conducted. Depigmented skin patches are a result of multifactorial action of autoimmune melanocyte dysfunction as well as genetic, oxidative autoinflammatory and neurogenic factors are involved. Standardized therapy of vitiligo is based on phototherapy and use of topical corticosteroids or calcineurin inhibitors, however new emerging methods of treatment have recently been introduced, including afamelanotide [44].

Considering the multiple effects of afamelanotide, it can present the adjuvant effect to UVB phototherapy [10]. It is observed that hair follicle melanoblasts are deprived of a melanocortin receptor system. NB-UVB stimulates undifferentiated melanoblasts and stem cells characteristic for hair follicle niche to express MC1R receptors making it ready for binding of afamelanotide. Therefore, according to the observations of an international group of researchers from the United States and France, afamelanotide may provide a direct source of α -MSH, acting on significant acceleration of the repigmentation process, previously induced and initiated by NB-UVB phototherapy. In 2013, this pilot study was conducted on 4 subjects suffering from vitiligo [45]. They were treated 3 times weekly with NB-UVB and, starting in the second month, received a series of 4 monthly implants containing 16 mg of afamelanotide. The study showed that afamelanotide induced faster and deeper repigmentation in each case and areas of repigmentation were observed within 2 days to 4 weeks after the initial implant, which increased throughout treatment to diffuse hyperpigmentation. Another study from 2015 is a randomized multicentre one and included 28 vitiligo patients with Fitzpatrick III to VI skin phototypes with a nonsegmental type of disease. It revealed that a combination of afamelanotide implant and NB-UVB phototherapy leads to statistically

significantly superior and faster repigmentation compared with NBUVB monotherapy (48.64% and 33.26% of repigmentation, respectively) [46]. Similar results come a study from 2020 on the Asian population, where combination therapy in 18 patients was superior to placebo, with a statistically significant decrease in the median Vitiligo Area Scoring Index scores for total, head and neck, hands, upper extremities, trunk, and lower extremities [47]. There is an ongoing open label, phase II study to assess the changes in pigmentation and safety of subcutaneous afamelanotide implants in the treatment of vitiligo on the face (NCT05210582).

Other rare and casuistic uses of afamelanotide in dermatology

The potency of the anti-inflammatory effect of afamelanotide was tested also in acne vulgaris in a case series [48]. In 3 patients with mild-to-moderate facial acne vulgaris, a dose of 16 mg afamelanotide was administered subcutaneously with a positive effect. The decrease in the total number as well as the number of inflammatory acne lesions was observed in all patients 56 days after the first injection [48]. The aetiology of acne is multifactorial and among different factors it also involves inflammation. In case of patients suffering from acne, anti-inflammatory and indirect antioxidative effects, observed for α -MSH in various experimental in vitro and in vivo models may contribute to the efficacy of afamelanotide. It was shown that α -MSH reduces secretion of chemokine IL-8 in the immortalized human sebocytes cell lines as well as it manifests a possible direct antibacterial effect against Gram-positive bacteria. It should be emphasized that limited trials of afamelanotide use regard mainly acne vulgaris, but the future utilization may also include hidradenitis suppurativa.

Promising data on the antioxidative properties of afamelanotide were published in 2 patients suffering from Hailey-Hailey disease with long-lasting lesions [49]. Clinical picture improved 30 days after the first injection of afamelanotide, and both presented 100% clearance of skin lesions 60 days after the first injection, independently of the skin lesion location.

It is also worth mentioning the beneficial effect of afamelanotide on reduction of DNA photodamage in xeroderma pigmentosum, announced in January 2023 (NCT05159752). Up to now, the CUV156 study confirmed the drug's ability to regenerate DNA of skin exposed to ultraviolet damage in 3 patients [50].

Afamelanotide is a convincing enriching, sometimes off-label, treatment option that physicians should take advantage of, however in diseases beyond EPP the further studies on a larger group of patients with long-term efficacy evaluation should be considered.

Conflict of interest

The authors declare no conflict of interest.

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