TECHNOLOGY UPDATE II

CLINUVEL

AFAMELANOTIDE AS AN ADJUNCT TO PHOTOTHERAPY

PHOTOTHERAPY – AN OVERVIEW

A number of severe skin disorders are treated by phototherapy, light therapy applied at certain wavelengths. The therapeutic effect of dosed light sources on a number of skin disorders such as psoriasis, polymorphous light eruption, solar urticaria and vitiligo is well demonstrated.

CLINUVEL is developing afamelanotide as a photoprotective agent in a variety of skin disorders, of which erythropoietic protoporphyria (EPP) is the indication most advanced in its clinical development. EPP is being treated as an injectable therapy during the spring and summer months, when UV intensity is highest.

Photodermatologists have long proposed that afamelanotide be used in combination with phototherapy to reduce the patients' exposure to radiation emitted by NB-UVB and to accelerate the melanogenic (pigmentary) response in severe skin diseases.

THE HISTORY OF PHOTOTHERAPY

In 1903, Prof Niels Ryberg Finsen, a Danish physician and academic, won the Nobel prize for his treatment of lupus vulgaris (a cutaneous mycobacterial or tuberculosis infection that causes lesions on the skin) using UV light. Finsen exposed his patients to concentrated sunlight and/or artificial light in hour long sessions to cause erythema which then resulted in the clearing of lesions. In the mid 20th century, William Goeckermann M.D., a dermatologist at the Mayo Clinic, introduced a combination of UVB and coal tar to treat psoriasis. This treatment known as "Goeckermann regimen" was one of the major therapies for moderate to severe psoriasis in the United States. In 1974, Dr John Parrish reported the use of a combination of an oral psoralen intake and subsequent UVA irradiation for psoriasis, introducing the concept of modern PUVA therapy. The US FDA approved the first NB-UVB devices for use in psoriasis in 2000 and in vitiligo in 2001.

PHOTOTHERAPY IN DEPTH

Phototherapy includes a variety of different treatment regimens, primarily: Broad-band UVB (BB-UVB), Narrow-band UVB (NB-UVB), UVA, UVA-1, PUVA and photodynamic therapy (PDT).

UVB is becoming the most frequently used therapeutic regimen for a variety of dermatoses. The need to separate the anti-psoriatic effects of the longer UVB wavelengths, around 311nm, from the potential side effects (such as sunburn) of the lower UVB wavelengths resulted in the development of NB-UVB therapy with the invention of 311 nm lamps. This specified band of light is known to deliver the same therapeutic effect and is believed to cause significantly fewer side effects.

Thus, UVB therapy is the primary focus of this update where 'phototherapy' is referenced.

BB-UVB radiation, with wavelengths ranging from 290-320nm, was the first phototherapy used in treating psoriasis, but its popularity decreased due to side effects – skin burn, photo-ageing and carcinogenesis (development of non-melanoma skin cancer) – which result from significant exposure of skin to wavelengths of less than 300nm.

The exact NB-UVB treatment regimen differs between physicians, but generally patients' skin is exposed to NB-UVB fluorescent lamps that deliver UVB light at 311 nm (+/-2nm). The initial starting dose (expressed in J/cm2) can be a fixed dose, or can depend on patient skin type or minimal erythemal dose (MED) determined prior to the treatment . Doses are increased by 10-20% at each session until: dose stabilisation; when MED is reached or the condition is determined to have resolved. When this stable dose is reached, the dose will be reduced to the last well tolerated dose and no further increments will follow. NB-UVB treatment is usually repeated 2-3 times per week on non-consecutive days. Sessions usually last for 5-10 minutes. The patients' eyes are protected with UV-blocking goggles and male genitalia and nipples are shielded with cloth and sunscreen containing zinc. Patients are advised to apply emollients and sunscreen daily.

CLINICAL RELEVANCE OF PHOTOTHERAPY

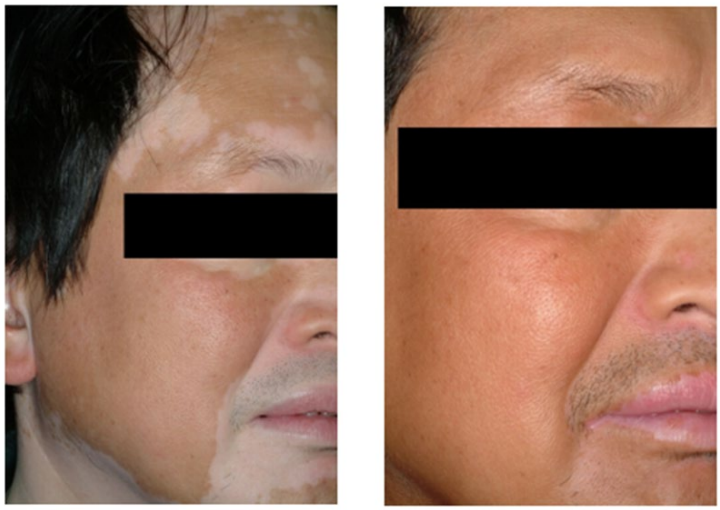
Phototherapy activates the epidermis and the pigmentary (tanning) response. In addition, NB-UVB stimulates the expression of factors that induces melanocyte migration. These may be important in a number of pigment-related diseases. Anti-inflammatory cytokines released upon UVB exposure may also contribute to the beneficial UVB therapeutic effects.

A number of side effects have been reported, such as erythema, pruritus and xerosis, but these resolve after topical application of emollients. Chronic effects of NB-UVB may include photoageing and photo-carcinogenesis; however due to the relative novelty of the therapy, chronic effects continue to be monitored. UVB is also known to induce other pro-inflammatory cytokines and photoproducts which can induce DNA damage; these are significantly reduced when light at 311nm is used.

In modern dermatology, NB-UVB is seen as a promising treatment for a range of diseases because it causes fewer side effects than the chronic exposure seen in other light treatments.

ADDITIONAL APPLICATION OF SCENESSE® (AFAMELANOTIDE 16MG)

Since NB-UVB causes the clinical effects of hyperkeratosis and melanogenesis (pigmentary response) in various diseases, it is anticipated that there will be a number of requests to use afamelanotide as a therapeutic treatment in several skin disorders (dermatoses). Such requests have lead to our first application of the drug in vitiligo.



Treatment of facial vitiligo with NB-UVB before (left) and after (right). NB-UVB has been shown to be an effective treatment for many patients with vitiligo (Photos provided courtesy of Pearl E. Grimes, M.D)

The advantage of a combination product (afamelanotide and NB-UVB) is expected to be a reduction in exposure to radiation emitted by NB-UVB and acceleration of the melanogenic response.

Read more about CLINUVEL's clinical program for generalised vitiligo.

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