Overview on Melasma and other Hyperpigmentations Using TCA PEEL with Moderator System

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Abstract
Melanoma remains a major cause of morbidity and mortality worldwide, however tremendous advances have been made in its treatment over the past several years. The discovery of genomic alterations that contribute to oncogenicity has ushered in a new era of molecularly-targeted therapy. Importantly, over half of melanomas harbor a mutation in the BRAF gene that leads to constitutive signaling down the MAPK pathway and multiple subsequent deleterious effects. Pharmacologic agents targeting this mutation have been developed and several are now FDA-approved, having yielded high response rates to therapy although these are tempered by a short duration of response. Multiple molecular mechanisms of resistance have been identified; however until recently few studies had delved into the immune effects of BRAF inhibitors. The effect of BRAF inhibition on anti-tumor immunity will be discussed herein, as will potential implications of these findings in the treatment of melanoma.

General Information
Cutaneous hypermelanoses are frequent concerns from patients in dermatology offices. Melasma, mottled dyspigmentation of photodamaged skin, “dark circles” of the periorbital skin, epheles, Postinflammatory Hyperpigmentation (PIH), cervical poikiloderma of Civatte are the most common hyperpigmentations that cause significant psychical and psychosocial distress. Despite the availability of a plethora of treatment possibilities - recalcitrant and recurring character of skin hypermelanoses are often frustrating for both patients and the clinicians.

Pigmentary disorders rank among the 5 most common skin complaints in several ethnic groups [1-3] but people of all races, skin types and ages might be affected. Treatment poses great challenges, especially in patients with higher Fitzpatrick - skin types [4]. Patients tend to ask for magic single treatment modalities without waiting time aiming to achieve complete and permanent removal of their dyschromias. The management is often challlenging regarding the limitations in efficacy, safety and costs of the currently available therapies. It needs extensive experience and good knowledge from the dermatologist as well as great deal of patience and strong compliance from the patient.

Hypermelanoses and other types of hyperpigmentations are asymptomatic but disfiguring disorders therefore have significant impact on the Quality Of Life (QOL) in many aspects of daily life [5]. As they cause considerable emotional and psychological distress - assessing the QOL is important in determining a treatment plan and it's efficacy, mainly because the physical health status may not correlate with the severity of the disease [6-7]. Physicians and patients must consider how to assess dyschromia: if the clinical examination is enough, or biopsy is needed as well, if colorimetry is necessary, and what are the exacerbating factors of the disease [8].

Successful treatment of hyperpigmentations typically involves a combination of topical agents with or without in-office procedures, taking the variable mechanisms of action of each treatment modality and topical agents into consideration [4]. The ideal bleaching agent has to fulfill certain pharmacological criteria and the treatment modality should have a potent bleaching effect with a rapid time of onset, carrying no side effects and lead to permanent removal of undesired pigment [9]. Hydrochinone (HQ) containing topical agents are the current standard for the treatment of melasma and many other hyperpigmentations - but concerns about the stability of it's formulations, side effects and long-term safety issues pushed efforts to develop alternative treatment options [10]. Besides the HQ containing gold standard triple combination with tretinoin and corticosteroids - azelaic acid, kojic acid, arbutin, ascorbic acid, glycolic acid (GA), trichloracetic acid (TCA), salicylic acid (SA) peels have also been tried with variable success [11]. Some typical promising agents include soy, rucinol, niacinamide, resveratrol, licorice, mulberry, elagic acid and dioic acid [12]. A multitude of novel topical agents with unique mode of action have been investigated for their potential as bleaching agents, however further studies are required to confirm their efficacy and safety before further recommendations. Oral agents like tranexamic acid and procyanidins are primarily used for the prevention of postprocedural hyperpigmentation [12]. The advances in fractionated photothermolysis, Intense Pulse Light (IPL), Q-switched lasers and newer chemical peels have widened the armamentarium of dermatologists for the treatment of pigmentary alterations. Still there is no unique modality in the treatment arena and further research is needed for discovering all the chemical reactions involved in the development of dyschromias. Expectations of patients often do not match the available treatment options, and one of the key roles of the dermatologist is to help the patient understand the biology of pigmentation, acquire the adherence to the best treatment recommendations and set realistic expectations. Further investigations are needed how to evaluate more in depth the QOL of people with dyschromias, which tools are needed to assess the dyspigmentation in daily clinical settings and when to introduce new treatment modalities during the course of management of pigmentary disorders.

Cutaneous hyperpigmentations mostly reflect to alterations in the melanin pigment in the epidermis, in the dermis or in both levels of the skin [13]. There are a group of diseases that have both congenital forms with different patterns of inheritance, and acquired forms related to cutaneous or systemic diseases [14].

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Melasma is one of the most frequently encountered acquired hypermelanosis affecting usually the facial skin. It is seen most commonly in women of child-bearing age with Fitzpatrick skin phototype III-V, living or having regular activities in areas or seasons of intensive UV light exposure. It occurs exclusively on sun-exposed surfaces, mainly on the face and occasionally on the forearms and on the neck. Men represent 10% of the cases [15]. The exact etiology of melasma is elusive, the pathogenesis is complex and the treatment is challenging. The two most important factors implicated in the development of melasma are exposure to UV radiation and genetic predisposition. Other classically implicated factors in the etiopathogenesis of melasma are pregnancy, exogenous female hormones, thyroid dysfunctions, administration of phototoxic drugs and cosmetics [16,17]. There are increasing evidences showing that melanocytes are not the only cells involved but other players also have key role in the promotion and relapses [18].

The distribution of the brownish-to-grey hypermelanotic patches show three distinct clinical patterns. 1. the most common centrofacial one involves the cheeks, nose, chin, frontal skin and the upper lip in 65% of the cases. 2. the malar pattern is responsible for 20% of melasma patients, affecting the cheeks and the nose. The 3. group involves the ramus mandibularis (15%) as mandibular pattern of the disease [14].

According to the histological findings, melasma has four histological types. In the epidermal type (70% of the patients) the pigmentation is intensified under Wood’s light examination where melanin content is increased in all epidermal levels. In the dermal type (10-15%) UVA light remains unchanged as many melanophages are seen throughout the dermis in histological preparations. Recent studies however questioned the diagnostic value of Wood’s light as the level of pigment deposit in the histological evaluation of melasma skin biopsies not always correspond to the Wood’s light findings - mainly in mixed type melanoma. Melanin in these cases increased in the epidermis, meanwhile many dermal melanophages are seen as well. UVA light examination has no diagnostic value in the indeterminate type of the disease - in patients with Fitzpatrick skin type - VI [14,17,19].

Immunohistochemistry findings of affected skin shows that the number of epidermal melanocytes can be similar or increased compared to the normal skin [20]. On the other hand the melanocytes exhibit characteristics of hyperfunctioning cells with enlarged size, prominent dendrites and intense staining [14,17]. The number of dermal melanophages and their melanin content is increased in the mixed and dermal type of the disease. Recent histological and immunohistochemical studies confirmed that melasma skin shows characteristics of chronic UV damage. Physiological reaction of the skin to UV irradiation involves a cascade of cellular interactions between a number of players like melanocytes, keratinocytes, fibroblasts, mast cells, inclusive vascular components of the dermis. As a consequence - dermal inflammation is supposed to have an important role in the development of hyperpigmentation and reactivation of melasma lesions [14,21-24]. In a recent study it is suggested that melasma skin is characterized by impaired stratum corneum integrity and delayed barrier recovery rate, related to downregulation of genes associated with lipid metabolism [25].

The target of melasma treatment is to inhibit the formation of melanosomes and promote their degradation, and to decrease the proliferation of melanocytes [14,26]. As there are increasing evidences showing that melanocytes are far not the only cells involved in the melasma development and relapses, and other players probably have key role in it - identifying the associated factors could provide new targets for more efficient treatment of melasma and better prevention of recurrences [18].

**First-line treatment** consists of rigorous broad spectrum photoprotection, combination of topical agents that target different pathways os melanin production, and effective cosmetic camouflage. **Second-line treatment** modalities consist of the addition of chemical peels to the above mentioned measures with critical approach for higher Fitzpatrick skin-types. Laser- and light therapies belong to the third-line therapeutic options for refractory cases but a higher risk for postprocedural hyperpigmentation is to be taken into consideration [27]. Photoprotection with SPF higher than 30, also with physical photoprotective agents is essential as lesions are aggravated by UVA, UVB and visible light as well. The gold standard melasma treatment includes topical HQ alone or combined with Retinoic Acid (RA) as double combination, or HQ plus RA plus a topical corticosteroid as triple combination [14,27,28]. The mechanism of action of the main depigmenting agents - like HQ, azelaic acid, arbutin, genicid acid, flavonoids, isoflavons, resveratrol, the AHA-s (alpha hydroxy-acids), the kojic acid, retinoids, niacinamid, soy-extract, Vitamins C and E, glabridin or the steroids are diverse. Therefore the combined therapies are mostly preferred to take the advantage of their synergism, achieving better efficacy with less adverse events [13,14,29,30]. For melasma cases refractory to topical treatment - the associated procedures with chemical peels and physical modalities like CO2 snow/cryo slush or dermabrasion/microdermabrasion is to be considered with special attention to the possibility of Postinflammatory Hyperpigmentation (PIH) [30]. Laser- and light therapies for the treatment of melasma became popular recently. Similar to chemical peels, device - based modalities carry an increased risk of adverse effects via direct damage to the skin and therefore a paradoxical increase of postprocedural dyspigmentation. It is mostly prevalent with darker skin types. Despite the risks mentioned above, there are promising published results on the third-line treatment modalities [29]. Treatment series with IPL for light skin patients without the history of PIH is a good alternative for dermal or mixed type melasma [31,32] however relapse rates are high. QS-Nd:YAG lasers seem to have detrimental effects on melasma with increase risk of PIH, relatively high rate of relapse and the possibility of excessive depigmentation [33]. Pulsed-Dye-Laser targets the vascular components of melasma [29] which is a promising new approach that has shown to delay relapses [34]. Fractionated photothermalisis is the only laser treatment that has been approved by U.S. FDA for the treatment of melasma as third-line therapy for severe cases who are ready to accept the risk of postlaser hyperpigmentation [17]. The use of newer anti-angiogenic lasers like copper-bromide lasers can be explained by the recent theory of the etiopathogenesis of melasma. It emphasizes the role of interaction between melanocytes and the cutaneous vasculature [35].

**Chemical peels** have been used for many years in the treatment of melasma, particularly in refractory cases. Studies evaluating chemical peels as monotherapy, in conjunction with/or versus other therapies for melasma have generally yielded variable results [29]. Chemical peels are increasingly popular methods for treating benign dermatoses like melasma because provide more rapid response compared to topical therapies.

**Chemical peeling** is the application of a chemical agent to the skin, which causes the controlled destruction of a part or of the entire epidermis with or without the dermis, leading to exfoliation and removal of superficial lesions, followed by regeneration of new epidermal and dermal tissues [36]. The mechanism of action in melasma is the removal of unwanted melanin via controlled chemical burn of the skin [37]. Peels are confirmed to be useful treatment modalities for melasma as monotherapy or as adjunct to topical treatments. Peels are used to...
treat the epidermal and mixed forms of melasma as the utilisation for
dermal or indeterminate histological types of the disease - generally
leads to unsatisfactory results or adverse events like permanent hyper-
or depigmentation and sometimes even to scarring [37]. The main
advantage of chemical peels are related to the fact that they can be
tailored for use according to the needs of the patient and can be used
synergistically with other in-office procedures and topicals. Chemical
peels for treating melasma maybe superficial or medium depth ones
[11]. Although peels can improve hyperpigmentary disorders by
removing unwanted melanin, they can cause irritation that might lead
to PIH, more commonly in patients with skin of colour. Therefore peels
- like other procedures causing injury to the skin - should be performed
with extreme caution for this subgroup of patients with melasma [27].

Alpha-hydroxy peels like glycolic and lactic acid, the beta-hydroxy
pel (salicylic acid), also the Jessner's solution, the Trichloracetic Acid
(TCA) and azelainic acid peels have been extensively studied for the
treatment of resistant melasma. Deeper peels are not used for this
indication because of high probability of dyspigmentation, scarring,
infection, persistent erythema and other associated complications
[11]. Glycolic acid peel (GA) is the most commonly used AHA peel in
30-70%. Both GA and lactic acids are thought to work also by
inhibitingtyrosinase activity in a dose-dependent manner [27]. Studies
with GA showed modest benefit in treating melasma and pretreatment
with HQ might enhance clinical improvement.

Lactic acid peels are studied for the treatment of epidermal melasma
compared to Jessner-peel in dark skin patients. It can be a safe and
moderately effective, low-cost alternative for this patient group.

Salicylic acid peel in 20-30% in ethanol solution is widely used
for higher phototypes in different hyperpigmentations with moderate
results and good safety profile. A new derivate of salicylic acid:
lipohydroxyacid has recently been introduced for the same purpose,
with a more targeted mechanism of action and a greater keratolytic
effect.

Trichloracetic acid peel (TCA) has a caustic mode of action as it
cogulates proteins that is detected by the phenomenon of "frosting".
It does not need neutralisation after application. The agent has no
absorption to the systemic circulation that defines it's systemic safety.
It is commonly used in lighter skin types but less frequently preferred in
darker patients due to the risk of post-peel dyschromias, and in extreme
cases of scarring [37]. Low concentrations of TCA (10-35%) is preferred
which reaches up to the upper papillary dermis - therefore TCA
peels are not effective enough for treating dermal forms of melasma
[38]. TCA peels were more extensively studied in different forms of
hyperpigmentation in light and also dark skin individuals. TCA in
varying concentrations can lead to a greater than 50% improvement
by clinical grading [39]. As medium - level concentrations of TCA (35-
45%) will penetrate between the superficial papillary and midreticular
dermis, there is an increased risk of PIH in dark-skinned patients using
higher TCA cc-s for deeper peels [12]. However focal application of
higher TCA cc-s were found to be effective in solar lentigos, freckles,
seborrhic keratoses and melasma without significant complications,
even with individuals of higher phototypes [39-47].

Jessner's solution (resorcinol/ salicylic acid / lactic acid) is extensively
used as superficial peeling for all skin types. Newer emerging peels
include tretinoin, pyruvic acid, mandelic acid, phytic acid and amino-
fruit-acid peels, however more studies are needed to evaluate their
efficacy and safety.

The most significant drawback of chemical peels - mainly in darker
skin types - is the potential for PIH and the relapses. Various measures
have been tried to overcome the problem, like maintenance chemical
peels, rigorous photoprotection and concomitant use of depigmenting
topical agents [37]. Preparation or priming of the skin before the
introduction of peels is one of the additional measure - for ensuring
more even penetration of the peeling agent, enhancing the healing and
maintaining the already achieved effects.

Chemical peels are promising modalities for the management of
melasma and other types of hypepigmentations - either alone or
adjunctive to topical treatment agents, however further studies are
needed for more experimentation [11,12,27,30,37].

The study was performed during January 2012 and December 2014
in various centers.

The Product

The product is a chemical peel called BRA from the Auriga
International laboratories associated with a home product called
Melaclear from the same company. In this article the peeling BRA will
be called the PEEL and Melaclear the HOME PRODUCT.

The chemical peel is an evolutive system containing TCA
(Trichroacetic acid) and a diluent hydrophilic solution. The system
allows the physicians to use the TCA in various concentrations (15, 30,
and 45% w/w). The mixture is done by the Physician in her/his office
just before the procedure. This mixture is chemically stable only for 20
hours.

The kit contains a 10 ml TCA 100% w/w water solution jar , the
dilution solution is presented in 3 bottle of 10 ml, a dropper and an
pipette which allow to realize accurate dilution. The innovation consists
of a strong antioxidant system (various polyphenols) which is present
in the dilution bottle and a TCA regulator which also allows very safe
applications of TCA on patient skin. The diluent solution contains
also as the home product the following ingredients: Phyric acid, free
Ascorbic acid 10% and complex mixture of polyphenols.

The peel can be applied in several layers without the risk of addition
of concentration as it is usual in TCA peel.

The studies were performed from January 2012 till December 2014.

History and Case Studies

A new formulation based on a synergistic activity between
vitamin c and phytic acid (addicted with a specific ro
modulator) for skin depigmentation: evaluation of efficacy
and safety

Dr. F. Angelis, Dr. J. Gallotti, Naples, Italy, 2008

Patients: 30 with hyper pigmentation disorders including melasma and lentigines: 10 patients treated with PEEL 15% formulation.

At home patients used HOME PRODUCT on the treated areas twice a day for 3 months.

- 10 patients used HOME PRODUCT only for a three months
  period time
- 5 patients with melasma were treated with a combination of
  PEEL 15% and 1540 fractional laser (1540 nm)
- 5 patients with lentigines x-were treated with a combination of
  PEEL 15% an IPL device.
Follow-up evaluations were conducted at one months, two months and three months.

Assessment:

a) Efficacy: Visual evaluation by the doctor and patients with a graduated scale using a range from 0 to 10.
   - 0 corresponds to the lack of improvement
   - 10 correspond to the complete restoration of the initial aspect of the skin.

b) Tolerance: Irritation, depigmentation of surrounding normal skin and post inflammatory hyperpigmentation.

Conclusion: In contrast with other topical agents that specifically acts on one step only, this formulation works blocking multiple steps during melanogenesis process.

Thanks to its chemical proprieties, this formulation is a real biomodulant agent. During the treatment we did not report any side effects. The association of Trichloroacetic acid, vitamin C and phytic acid is a first choice treatment during summer and we recommend using it in combination with other topical treatments or lasers due to its good compliance to improve results.

In addition, repetitive sessions might constitute an effective approach to depigmenting process when using the topical agent alone, while combination treatments with lasers may obtain faster, safer and long lasting result

Effectiveness and safety of treatment with 15% TCA skin peel containing phytic acid and l-ascorbic acid for skin pigmentation in asians

Objective: The aim of this study is to evaluate the effectiveness and tolerance of a skin peel product containing 15% TCA combined with phytic acid and L-ascorbic acid in the treatment of pigmentation disorders in Asian skin.

Patient and method: The study includes 10 patients (aged between 30 and 56) with pigmentation disorders. The skin types studied were categorized as between III and IV according to the Fitzpatrick classification.

The skin peel product used in the study contains the following ingredients: 15% TCA, 2% phytic acid, 10% L-ascorbic acid, Camellia Sinensis leaf extract, Vitis Vinifera seed extract, glycerine, alcohol, ethoxy diglycol and water.

For each patient, the skin peel product was applied twice, with an interval of 3 weeks. At home, patients applied the same product, but without TCA (HOME PRODUCT) twice a day for three months after the first visit.

The pigmentary lesions were evaluated at the beginning and at the end of the Treatment using the optical system Dr M. Tosa, The Mayumi Clinic, Japan, 2009 (Figures 1-5).

Results: With regard to tolerance, 3 patients presented severe redness after the first session, which led to their premature exit from the study.

The remaining 7 patients suffered no intolerance problems during the two sessions and continued to participate in the study.

With regard to effectiveness, evaluation of the therapeutic response
showed a clear improvement in pigmentation disorders in the 7 patients, with a marked anti-aging effect.

**Conclusion:** The effectiveness of this skin peel (15% TCA combined with phytic acid and L-ascorbic acid) was demonstrated on Asian patients suffering from pigmentation disorders. This effectiveness was combined with great tolerance on this type of skin sensitive to TCA.

**Evaluation of the effectiveness and tolerance of peel containing 15% concentration of TCA**

Dr. J. David, Paris, France, 2010

**Objectives:** The aim of this study is to evaluate the effectiveness and tolerance of a skin peel product containing 15% TCA.

Analysis focused on pigmentation, complexion tone, skin softness and texture, facial radiance and wrinkles.

**Patients and Methods:** The study includes 10 patients (aged between 31 and 72).

The PEEL product used in this study had a 15% concentration of TCA. For each patient, the product was applied 3 times, with intervals of 8 to 10 days between each session.

During the study, all treatments that might have interfered with the study were excluded.

The evaluation of this study focussed on the effectiveness and tolerance of the PEEL in each patient, and also on analysis produced using Antiaging SD software.

**Results:** With regard to tolerance, some patients experienced irritation and a sensation of warming during the session. 8 and 15 days later, tolerance was excellent (Table 1 and Figure 6).

With regard to effectiveness:

**Conclusion:** PEEL is clearly effective in improving skin texture and in reducing sebum and pigmentation marks. Skin is more radiant and glowing. Wrinkles and fine lines are reduced and pores tightened.

**Case Studies**

**Treatment of melasma** (Figure 7)

Dr. B. Blouard, Belgium, 2011

**Evaluation of the depigmenting effect of peel product combined with home product on lentigo and melasma**

Dr. E. Duray, Hungary, 2013

**Objectives:** The aim of this study is to evaluate the effectiveness and tolerance of PEEL in the treatment of lentigo and melasma on different parts of the body.

**Patients and Methods:** The study includes 20 patients presenting with pigmentation disorders (lentigo or melasma) on different parts of the body. The skin types studied were categorized as between II and IV according to the Fitzpatrick classification.
With regard to effectiveness, the evaluation of the therapeutic response demonstrated a clear improvement in pigmentation disorders, sometimes even a complete disappearance of pigmentation marks.

**Conclusion:** The effectiveness of PEEL evolutive peeling has been demonstrated on patients suffering from pigmentation disorders. Several sessions proved necessary.

PEEL treatment resulted in an almost complete, even complete, disappearance of lentigo and melasma.

The operator can apply the higher concentrations (45%) individually to lentigo and melasma using a cotton bud.

Each patient was given 3 applications of the product. Sessions were at 10 to 20 day intervals. At home, patients applied HOME PRODUCT twice a day. Pigmentary lesions were evaluated at each session.

Evaluating the effectiveness of PEEL was carried out by both patient and doctor (Figures 8-11).

**Mode of Action of this System on Pigmentation**

Pigmentation is a complex process including oxidation in several pathway of the melanin synthesis.

Most of the products available nowadays on the market from pharmaceutical and cosmetic industries are only partial tyrosinase inhibitors and contain very often only one active ingredient. As we know the process of pigmentation involved several steps (Figure 12), such as dendrites transfer for the melanin, DHCA, and other oxidation process and turnover of corneocytes.

In conclusion an efficient product or a physical treatment (lasers, peeling …) must work on the different steps of pigmentation.

**General Conclusion**

The review of the literature mentions good results with TCA peeling but also with frequent recurring pigmentation and the postprocedural PIH. The present review study shows clearly that we can avoid these problems with the use of this new peeling. The explanation can be in the two main following innovations.

![Figure 8: Women (aged 64) treated for melasma](image1)

![Figure 9: Woman (aged 44) treated for melasma.](image2)

![Figure 10: Woman (aged 60) treated for lentigo.](image3)

![Figure 11: Woman treated for melasma.](image4)

The skin peel product used in the first session of this study had a 15% concentration of TCA and 30% in the 2 subsequent sessions.

**Results:** With regard to tolerance, patients experienced no intolerance problems throughout the various applications in the study. Sensations experienced during sessions were for the most part a warming of the skin and a slight stinging.

During sessions using concentrations of 30% and 45% TCA, freezing occurred and skin became red, irrespective of the concentration of TCA.
The first is the combination of TCA with a strong anti-oxidant composition in the dilution product. The second advantage of this system is also the presence of a TCA moderator which allows applying several layers of the peeling during the same séance and certainly on different composition in the dilution product. The second advantage of this system is also the presence of a TCA moderator which allows applying several layers of the peeling during the same séance and certainly on several layers of the peeling during the same séance and certainly on different skin conditions and concerns in South Asian Americans: a community-based study. J Drugs Dermatol 10: 524-528.


