Correction to: Vitiligo

Mauro Picardo and Alain Taïeb

Correction to:
M. Picardo, A. Taïeb (eds.), *Vitiligo*, https://doi.org/10.1007/978-3-319-62960-5

Owing to an unfortunate oversight a preliminary version of the book was inadvertently published. The most important corrections are:

1. Permission for using the table 11.1 had been acquired from Pigment Cell Melanoma Res (not Pigm Mel Research). Hence, caption for Table 11.1 has been corrected to "van Geel N, Speeckaert R, Taieb A et al. Koebner's phenomenon in vitiligo: European position paper. Pigment Cell Melanoma Res 2011; 24: 564–73. With permissions from Pigment Cell Melanoma Res (not Pigm Mel Research)"
2. Dr. Gisela F. Erf was inadvertently omitted as a contributor to chapter 28. The correct order of authors is as follows:
   Webb, K. C., S. W. Henning, G. F. Erf, and I. C. Le Poole
3. An outdated version of text had been used in section 35.1.2 in chapter 35 "Topical calcineurin inhibitors" and the correct version is below.

Topical calcineurin inhibitors

J.E. Lommerts, A. Wolkerstorfer, N. van Geel, M.W. Bekkenk

Background

The topical calcineurin inhibitors (TCI)- tacrolimus ointments 0.1% and 0.03% and pimecrolimus cream 1%- have been specifically developed for the treatment of atopic dermatitis, but are used for a wide range of inflammatory disorders. In contrast to topical corticosteroids (TCS), TCI do not have the risk of local

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M. Picardo (✉)
Cutaneous Physiopathology & CIRM, San Gallicano Dermatological Institute, Rome, Italy

A. Taïeb
Hôpital Saint André, Service de Dermatologie Adulte et Pédiatrique, INSERM U 1035, Université de Bordeaux, Bordeaux, France

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side effects related to skin atrophy, telangiectasia, and glaucoma after prolonged use. Therefore they are preferentially used in areas more susceptible to these side effects, such as head and neck region.[1, 2] Furthermore, because of the limited percutaneous penetration through intact skin, significant systemic absorption has not been reported following normal use.[3] Tacrolimus and pimecrolimus are topical immunomodulating agents (derivative of ascomycin macrolactam), that inhibit calcineurin. By inhibiting the release of various Th1 and Th2 type cytokines, such as TNFα it can influences the activation and maturation i of T-cells. This has led to speculate that this mechanism may interact with the process leading to melanocytes loss in lesional skin of vitiligo lesions. The inhibition of TNFα production was suspected by some authors to be especially important in vitiligo, as TNFα can inhibit melanocyte proliferation and melanogenesis, and that it can induce ICAM-1 expression on melanocytes, through which T- lymphocyte induced destruction of melanocytes may occur.[4] In addition, in vitro studies[5, 6] also have shown stimulating impact of TCI on melanocytic migration and growth.

Efficacy

Monotherapy with TCI

To date, several clinical studies have investigated the efficacy of topical monotherapy with either pimecrolimus or tacrolimus in vitiligo.[4, 7–22] In a randomized controlled trial, Ho et al.[22] showed that tacrolimus 0.1% ointment twice daily was effective after 6 months in approximately 60% of lesions on the face and in 23% of lesions on the rest of the body. Furthermore, Radakovic et al.[21] showed moderate tot excellent responses (>25% repigmentation) in 27% of the patients after tacrolimus 0.1% ointment 1-2 times daily. In another randomized clinical trial tacrolimus 0.1% ointment was shown to be as effective as 0.05% fluticasone proprionate cream after a follow-up duration of 6 months.[20] Kose et al.[19] compared pimecrolimus 1% cream twice daily with mometasone cream 0.1% once daily in childhood vitiligo. In 45% of patients treated with pimecrolimus a decrease in lesion size was found and in 3 patients complete remission was achieved. Dawid et al.[18] investigated in a randomized clinical trial the lesion size of vitiligo patients treated with either pimecrolimus 1% cream or placebo and found a decrease of 90 mm2 vs 220 mm2, respectively, however this difference was not significant. Pimecrolimus 0.1% cream under occlusion once daily with or without microdermabrasion was more effective than placebo in the study of Farajzadeh et al.[17]. Several case series also published the efficacy of topical tacrolimus and pimecrolimus in vitiligo. [4, 7–10, 12–16] Lepe et al. assessed the efficacy of topical tacrolimus 0.1% vs topical 0.05% clobetasol proprionate in childhood vitiligo and after 2 months mean repigmentation of 41.3% and 49.3% were found, respectively[11] Data about the most effective treatment scheme using TCI in vitiligo are still missing. In the available vitiligo studies the application frequency is varying between once and twice daily for both pimecrolimus and tacrolimus application. Twice daily application of tacrolimus seems to be more effective than once daily.[21, 23] Several studies have shown that the efficacy of topical pimecrolimus and tacrolimus is higher when applied on the face than on other locations.[4, 7, 9–11, 15, 19, 21, 22, 24] Duration of treatment ranged in most of the studies from several weeks to 1.5 years and information about the minimal or ideal treatment period in vitiligo is not available. However, intermittent use after repigmentation, on the model of proactive treatment of atopic dermatitis, has proven to be helpful to limit relapse in a controlled study[25] and repeated application may limit Koebner's phenomenon[26].

Combination therapy of TCI and phototherapy

To enhance repigmentation in vitiligo lesions the combination of TCI and phototherapy is frequently used in daily practice as the combination therapy is thought to play a synergistic role.[27] Furthermore, in the past years several studies[24, 28–32] showed the efficacy of combination therapy of TCI and phototherapy. In a randomized clinical trial, Esfandiarpour et al.24 compared the efficacy of narrowband UVB phototherapy three times weekly with and without pimecrolimus 1% cream. After 3 months of treatment the combination of narrowband UVB phototherapy with topical pimecrolimus application was significantly more effective than nar-

rowband UVB alone. Dayal et al. 28 showedtthat combination of narrowband UVB with tacrolimus 0.03% was significantly more effective than phototherapy alone in childhood vitiligo. Furthermore, a meta-analysis showed that lesions located on the face and neck show better results with combination of narrowband UVB phototherapy and TCI than narrowband UVB phototherapy alone.[33] This improved efficacy of the combination was found for both ≥50% repigmentation (RR = 1.40, 95% CI 1.08-1.81) and ≥75% repigmentation (RR = 1.88, 95% CI 1.10-3.20) In a randomized placebo-controlled study of Mehrabi et al.[31], narrow-band -UVB therapy with and without tacrolimus ointment was compared and no additional effect of tacrolimus was found. However, a low number of study participants (n=8) was included and the evaluated lesions were all located on non-facial areas. Systematically congregated evidence in the systematic review of Bae et al.[34] showed that the combination of 308-nm excimer laser therapy with either topical pimecrolimus or tacrolimus application is more effective than excimer laser therapy alone (4 studies, relative risk 1.93, 95% confidence interval 1.28-2.91).[34] These results were confirmed in childhood vitiligo in a recent randomized controlled trial of Li et al.[35]

Side effects

The most common reported side effects for TCI within the first days of treatment are local reactions such as burning sensation, pruritus, and erythema. This seems to be less frequently reported compared to atopic dermatitis.[17, 20, 30] A possible explanation for the latter might be the difference in skin barrier between both diseases. Based on some studies in atopic dermatitis no significant increased risk for skin or systemic infections could be demonstrated.[36–39] Tacrolimus-induced lentigines and hyperpigmentation in vitiligo lesions of the infraorbital area are rare side effects that have been related to sun- and UV-exposure.[38, 40] Less frequently reported side effects in the face are acneiform eruptions and hypertrichosis.[39] The FDA announced a black box warning in 2006 for the application of tacrolimus and pimecrolimus, including concerns of potential safety issues (e.g. risk for skin cancer and lymphoma). So far the use of TCI has not been reported to be associated with significant systemic immunosuppression or increased risk for skin cancer and other malignancies in clinical vitiligo trials. Moreover, in contrast to atopic dermatitis the barrier of the skin in vitiligo is not disturbed, so less absorption can be assumed. Furthermore, a recent study found that in atopic dermatitis in more than 25,000 person-years of follow-up no association was found between occurrence of malignancy and use of TCI.[41] Therefore, the risk on skin cancer and other malignancy in vitiligo after application of TCI is considered to be very low. However, in vitiligo the TCI are often used in combination with UV therapy. This may lead to a potentially higher risk for skin cancer and conclusive data on the safety on the combination therapy of TCI and phototherapy is still lacking.

Interpretation and recommendations

Although the quality of the evidence for the efficacy of TCI in vitiligo is limited, topical pimecrolimus and tacrolimus are widely recommended in national and international guidelines for vitiligo based on expert based opinions and experience.[42–44] The repigmentation of TCI in vitiligo varies according to the anatomical location of the lesions. Most studies show favourable results mainly in the area of head and neck.[45] This is probably linked to the presence of melanocytes in remaining pigmented hair follicles. Besides, the influence of a reduced epidermal thickness might be of importance as this facilitates penetration of large molecules such as TCI into the skin. Moreover, the head and neck region is a UV exposed region of the body area and UV therapy is a therapy of vitiligo which could play a synergistic role. Most studies included repigmentation as their primary outcome. It can be discussed whether cessation of spreading of the depigmentation would have been a better primary outcome to measure the efficacy of TCI as repigmentation does not always occur in vitiligo after topical treatment alone. A correlation between the repigmentation rate and patients' age or duration of the disease has not been consistently demonstrated. According to some reports, the efficacy of TCI

in childhood vitiligo seems to be comparable to that in adult patients.[1, 7, 11, 45]

In summary, based on the available literature TCI can be recommended for treatment of depigmentations on the face and neck in both children and adult patients with vitiligo. TCI are also used for long-term control of the disease because of their efficacy and limited side effects compared to potent topical corticosteroids. Superior effect of the combinations with natural light of UV phototherapy has been demonstrated, although conclusive data related to the safety aspects are still required

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4. A section on Tissue Grafting in chapter 36, "Surgical Therapies" had been missed out and the text has been included below.

Tissue grafting for Vitiligo

Contributed by Kanika Sahni, Assistant Professor, and Dr. Somesh Gupta, Professor, Department of Dermatology & Venereology, All India Institute of Medical Sciences, New Delhi, India

Tissue grafting procedures involve transplantation of skin and/or hair follicle grafts directly from donor site to recipient site. This may involve minor modifications to the tissue but no chemically induced modification.

Tissue grafting procedures may be subclassified into:

1. Pure epidermal grafts: These have the advantage of minimum scarring or postinflammatory changes at donor site and excellent texture match at recipient site
   (a) Suction blister grafting
   (b) Ultra-thin STSG
2. Dermo-epidermal grafts: As these grafts involve damage to superficial dermis they are often associated with scarring at donor sites and poorer textural match at recipient site
   (a) Mini punch grafting
   (b) Split thickness skin grafts
   (c) Mesh grafting
   (d) Smash grafting
3. Hair follicle grafting: This technique is particularly useful for hair bearing areas with leukotrichia including scalp, eyebrows and eyelashes.

Suction blister epidermal grafting (SBEG)

This technique involves the use of negative pressure to create blisters at donor site followed by utilization of the roofs of these suction blisters as a graft to cover the dermabraded recipient site. This technique leads to creation of a split at the dermoepidermal junction, being the weakest among all layers of skin, thus providing a purely epidermal graft which follows the concept of "recipient dominance". This implies that the graft

takes up the colour and texture of the recipient site in contrast to thicker dermoepidermal grafts which follow the concept of "donor dominance". Thus these grafts tend to provide better cosmetic outcome especially on cosmetically important sites like lips, areolae etc. Another advantage is the absence of scarring or textural change at the donor site, which allows repeated harvesting from same donor site.

The use of this technique was first described by Falabella for treating depigmented and granulating areas such as vitiligo and chronic wounds.1 The technique has undergone various modifications and the currently widely used method of creating blisters was pioneered by one of the authors (SG).2,3

Technique

Blister induction

The blisters are usually created on a hidden area of skin, either the lateral upper thigh or upper inner arm. We recommend to use the area on the lateral thigh just below the trochanter of the femur as the tense skin and underlying bone provide a good surface for rapid induction of blisters. The patient is made to lie down in lateral position and the donor area is cleansed and anesthetized by a field block using a mixture of bupivacaine (0.5%) and lignocaine (2%) in a 1:3 ratio in order to provide long lasting anesthetic effect. The site is then lubricated with white petroleum jelly, which forms an impermeable layer between suction syringe and the skin surface.

Depending on the size of recipient area, 10-ml syringes are prepared by removing the plunger and attaching the three-way cannula to the hub of syringe. The three-way cannula is placed vertically to allow the syringe to communicate with the air at one end of cannula only. One by one these syringes are placed on the skin surface with the broad end in good contact with the skin. The assistant then attaches a 50-ml syringe to the communicating end of the three-way cannula and pulls the plunger up to a volume of 25 to 30 ml to achieve a vacuum of −300 to −400mm Hg. The surgeon then rotates the three-way cannula lock to a horizontal position in order to cut off the communication of 10-ml syringe with the external air. This allows the maintenance of the vacuum hence created and results in a dome-shaped elevation of the donor skin visible inside the lower end of the syringe. Remaining syringes are applied in a similar manner half to one centimetre apart.

The patient is asked to lie down in the same position for around 2 to 3 hours which is the usual suction blister induction time. Once the blisters are formed, the suction is released by rotating the lock of the 3-way cannula and the syringes are removed.

Harvesting of grafts

Once the blisters have formed, with the help of a pair of curved scissors, the roofs of the blisters are cut all along the margins of the blister except one edge and transferred onto sterile glass slides (with antibiotic cream smeared on it) with the dermal side of blister facing up. After this the remaining attachment of the blister is also cut and the grafts are spread with the help of a blunt forceps to remove any wrinkles and strands of fibrin. The grafts are kept moist by placing in a sterile tray containing normal saline. These pure epidermal grafts are then transferred onto the dermabraded recipient site with the dermal side facing down. It is very important to place the grafts with the correct side facing down, as an upside down placed graft would lead to failure of repigmentation. The donor site is dressed with sterile non-adherent chlorhexidine gauze (Bactigras®) and a layer of dry gauze kept in place with micropore tape. The patient is asked to keep the area dry and remove the dressing after 3 days.

Preparation of recipient site

The vitiligo patch to be treated is cleaned, draped and anesthetized using 1% lignocaine buffered with sodium bicarbonate. This is followed by dermabrasion using either a manual or a motorised dermabrader upto the level of dermoepidermal junction which is recognized by the appearance of tiny pin point bleeding points. The dermabraded sites are covered with a saline-soaked gauze to assist in hemostasis. Then the suction blister epidermal grafts are transferred

onto the dermabraded sites by placing the slide upside down and gently removing the slide while leaving the grafts (dermal side down) on the denuded surface. The grafts are then gently spread to their maximum size by using a fine forceps in order to cover the largest area. Successive grafts may be placed adjoining each other or 0.5-1 cm apart as pigmentation from each graft is expected to spread around 0.5-1cm beyond the graft margin.

The area is dressed with sterile non-adherent chlorhexidine gauze (Bactigras®) followed by a layer of dry gauze which is kept in place with elastic adhesive bandage (Dynaplast®). Patient is asked to keep the area dry and prescribed oral antibiotic and analgesic medications for a week after which the dressing is removed. The grafts are visible as dry pieces of skin and may fall off soon after, however a period of 1 week is sufficient for the melanocytes to transfer from the graft onto the recipient site. The patient is then asked to initiate phototherapy and the spread of pigmentation occurs over the next 3-4 months (Fig. 1). Often, the grafts come out as thin, dry membrane, leaving behind faint pigmentation which, in due course, darkens and covers the entire area. Epidermal grafts act as melanocyte-keratinocyte carrier.

Modifications of technique

A number of other methods for induction of blistering have been described including the use of suction cups attached to a respiratory suction apparatus, Chinese cupping technique and few other tech-

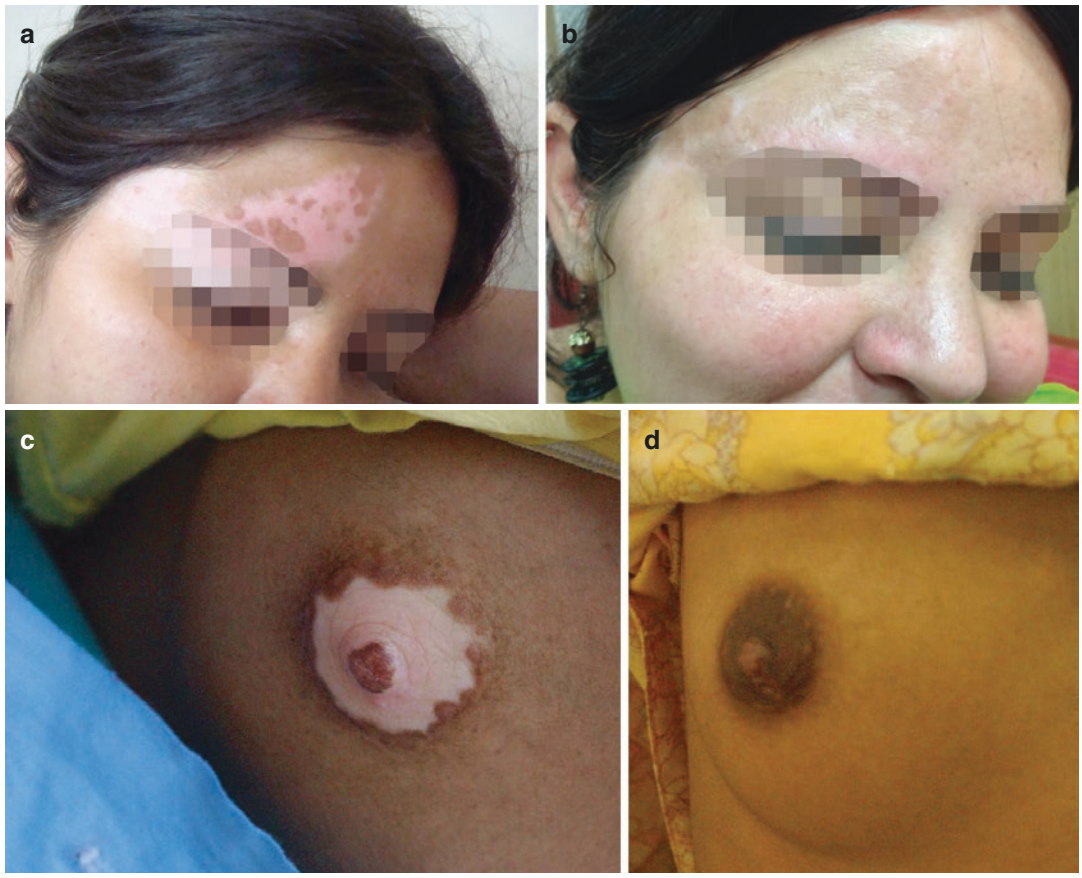

Fig. 1 (**a**) before suction blister grafting in a patient with mixed vitiligo. (**b**) after grafting. (**c**) Acrofacial vitiligo on nipple and areola. (**d**) complete repigmentation after suction blister grafting

niques.4,5,6 Various factors have been shown to affect the blister induction time such as the strength of negative pressure applied, the size of the suction cup/ syringe and the temperature with a higher temperature of 40°C hastening the blistering process.7,8,9 This has also been confirmed in a recent in vitro study on optical coherence tomography in induced suction blisters.10 The size of partially formed blisters may be expanded by inserting saline into the blister cavity by introducing a needle into the cavity through its floor.11Another modification is the use of transparency sheets instead of glass slides to transfer the grafts; however as glass slides are readily available we recommend their use for this purpose.

The preparation of the recipient site may be done in several other ways, using CO2 laser dermabrasion, Er:YaG laser dermabrasion, suction blister induction on donor site, liquid nitrogen cryofreezing, and phototoxic induction of blisters.4612,13,14,15

Modifications are also required depending on the location of vitiligo patches. Stay sutures or tissue glue are recommended to hold the dressing in place following surgery for lip vitiligo. Patients are asked to take liquid diet with straw for a week until the dressing is in place in order to avoid soiling of the dressing. For lesions on fingers and toes, results may be improved by good immobilization of the operated area using a plaster of Paris slab.

Results

The dressings are removed after one week and this time is sufficient for the melanocytes to take up in the recipient skin from the SBEG. Thus, even if the grafts are lost at the time of removal of dressing, it is not a cause of concern as transfer of melanocytes has already occurred. Repigmentation is noticed within a few weeks and if followed by phototherapy to the site, there is significant spread of pigment around the graft margins which results in repigmentation of the intergraft areas also.

In a large study on SBEG by Gupta *et al*., results were found to be significantly better in segmental/focal vitiligo where 91% patients achieved successful repigmentation) compared to 53% patients of generalized vitiligo. Another factor predicting better response included age younger than 20 years. No significant difference was found in results based on body site treated or the period of stability if it was more than 1 year.16 SBEG has been found to be inferior to both non-cultured epidermal suspension (NCES) transplantation and STSG in two different comparative trials while results were comparable to punch grafting and cultured melanocyte transplantation in another study.17,18,19

Complications

Most adverse events of the procedure are mild. Patients often report discomfort and pain during blister induction which may be lessened by infiltrating the area with long acting local anesthetics such as a combination of bupivacaine and lignocaine prior to the procedure. The donor site heals without textural change or scarring in most patients, however, hyperpigmentation may persist for few months with gradual lightening. Less common complications at donor site include Koebner phenomenon and secondary infection. At the recipient site, secondary infection, scarring, keloid formation and hyperpigmentation have been reported infrequently. Unlike, STSG or punch grafting, there is no stuck-on appearance, wrinkling or cobblestoning and the technique offers excellent cosmetic outcome even on facial and mucosal lesions.

Mini punch grafting (Minigrafting)

This is one of the oldest and simplest techniques described for the treatment of vitiligo, however, it is often associated with risk of variegate repigmentation and cobblestone appearance. Early studies reported the use of larger sized punches (2-3mm) which were associated with a higher risk of cobblestone appearance, hence the current recommendation is to use smaller sized punches (1-1.5 mm).

Technique

It is ideal to choose a donor site on a hidden area where the skin has nearly similar dermal thickness as the recipient site. For facial lesions, it is ideal to harvest punches from the retroauricular skin and for other areas, any other hidden site like inner arms or thighs may be used. After cleaning

and draping, the donor and recipient sites are anesthetized using lignocaine with adrenaline. After this, punches of size 1-1.5 mm are harvested first from the recipient site in order to create chambers where punch grafts will be placed. These are created first along the margin of the vitiligo patch followed by other parts of the patch at a distance of 0.5-1cm from each other. After this, 0.8-1mm sized punch grafts are harvested from the donor site using disposable biopsy punches and placed in a petridish containing normal saline. Once the chambers at recipient site have stopped bleeding, the grafts are placed with the dermal side down in them in such a manner that the upper surface of the graft lies at the level of the surrounding skin in order to prevent cobblestoning. The area is dressed using non-adherent antibiotic coated sterile gauze followed by a layer of gauze and bandaged. The dressing is removed at day 8 followed by phototherapy to aid in pigment spread. Modifications of the procedure include use of motorized punches and use of tissue glue to fix the grafts in place.20

The technique is simple to perform and can be used easily in limited resource settings. It is also considered to be one of the treatments of choice for vitiligo on tips of fingers and toes and to treat small residual patches remaining after prior surgery. Risk of cobblestoning can be minimized by careful technique and smaller sized punches. The technique is also useful while assessing patient's suitability for surgery in patients with doubtful stability, in the form of test grafting where perigraft spread of pigment is considered to be indicative of good prognosis following surgery.

Results

In a review on minipunch grafting, there is significant difference in size of punches used for surgery, with most earlier reports using 3-4mm punches with the trend now being more in favor of smaller (1-2mm) sized punches (Fig. 2). Onset of repigmentation occurs as soon as 14 days after transplantation and pigment spread beyond margin of grafts has varied from 1-15mm in different studies.21 A study comparing the results of MPG with transplantation of extracted follicles, no significant difference in repigmentation was observed between the two groups. 22

Hair follicle grafting

This may be considered as a modification of minipunch grafting. This technique is suitable for hair bearing sites like scalp, eyebrows and hair bearing areas on the body. This technique involves harvesting of follicular unit grafts from the scalp by the technique of follicular unit extraction (FUE) or strip harvesting followed by implantation onto slits or punches created on the hair bearing vitiligo patches. This technique may also be used on hairless sites, by removing the hair bulb before transplanting the extracted follicular unit. Recently body hair transplantation has also been described for the treatment of vitiligo.23

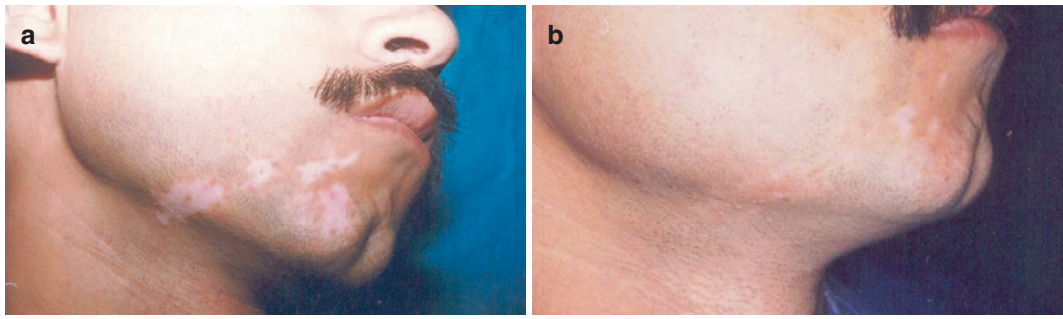

Fig. 2 (**a**) before suction blister grafting in a patient with mixed vitiligo. (**b**) after grafting

Thin and ultra-thin split thickness skin grafting (STSG)

Split thickness skin grafting involves the harvesting of a thin sheet of epidermis from a covered part of the body followed by transplantation onto dermabraded vitiligo patches. The grafts may be harvested either manually using a Humby's knife or Silver's knife or using motorized dermatomes like Davol's dermatome or Zimmer's dermatome.

Technique:

The donor site is chosen over the thigh, buttocks or upper arms and is first cleaned, draped and anesthetized using a field block using lignocaine. Alternatively topical anesthesia has been used in some patients providing adequate pain relief without the need for injectable anesthetics. A thin slice of skin is harvested using either a Humby's knife or alternatively motorized dermatomes like Davol's or Zimmer's dermatome may be used to harvest ultra thin skin grafts. The motorized dermatomes have the advantage of harvesting larger sized nearly pure epidermal grafts which provide better textural match.

The recipient site is dermabraded and the STSG is placed on it with the dermal side down followed by dressing with non adherent gauze dressing.

A modification of the technique which can allow covering of larger surface area is "mesh grafting" in which either manually (by creating slits with a blade) or using a specialized apparatus (Ampligreffe®), the graft is meshed to expand it in a ratio of 1:1, 1:2, 1:4, or 1:6. This allows for larger surface area to be covered.24,25

Results

A study on STSG in 32 patches of stable vitiligo found that 100% repigmentation was achieved in 22 patches and 90-95% repigmentation in 10 patches.26 In a recent study in 40 patients with stable vitiligo, a combination of UTSG followed by NBUVB therapy yielded more than 90% repigmentation in 83% of patients.27

Complications

Due to slightly uneven thickness of harvested graft with varying amounts of dermal tissue, there may be stuck-on appearance cosmetic result may be inferior to that with purely epidermal grafts or with cellular grafts. This is less likely to occur with grafts harvested using motorized dermatome. A thicker graft is also likely to heal with more prominent scarring at the donor site.