Vitiligo

Number: 0422

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers the following established methods medically necessary for the treatment of vitiligo:

- Excimer laser (e.g., XTRAC, PhotoMedex, Radnor, PA; EX-308, Ra Medical Systems, Inc., Carlsbad, CA)
- Narrow-band ultraviolet B (UVB)
- Topical and oral psoralen photochemotherapy (PUVA)
- Topical tacrolimus
- Topical and systemic corticosteroids

Aetna considers continued PUVA or narrow-band UVB therapy not medically necessary unless there is significant follicular pigmentation after 6 months of therapy (8 to 10 treatments per month).

Aetna considers treatments for vitiligo cosmetic if they do not affect the underlying condition and do not result in improved protection against skin cancer; specifically micropigmentation (tattooing) and depigmentation (with monobenzylether of hydroquinone/monobenzone) are considered cosmetic.

Policy History

Last Review
07/05/2019
Effective: 06/20/2000
Next Review: 04/24/2020

Definition

Additional Information

Clinical Policy Bulletin
Notes
Aetna considers Apal, BsmI, catalase (389C>T), cytotoxic T-lymphocyte antigen (CTLA)-4+49A/G, human leukocyte antigen-A, NLRP1, protein tyrosine phosphatase, non-receptor type 22 +1858C→T, and TNF-alpha-308G/A gene polymorphisms testing for early detection of vitiligo experimental and investigational because their effectiveness has not been established.

Aetna considers the following interventions experimental and investigational for the treatment of vitiligo because their effectiveness for this indication has not been established (not an all-inclusive list)

- Apremilast
- Autologous mini-punching grafting
- Blister roof grafting (suction epidermal blister grafting) (e.g., CelluTome Epidermal Harvesting System)
- Capecitabine
- Carbon dioxide fractional laser
- Chimeric monoclonal antibody to CD20 (e.g., rituximab)
- Glutathione
- Home phototherapy
- Interleukins
- Janus kinase inhibitors (e.g., ruxolitinib and tofacitinib)
- Melagenine
- α-melanocyte stimulating hormone (e.g., afamelanotide)
- Melanocyte transplantation/cultured and non-cultured cellular melanocyte keratinocyte transfer
- Neovir (an intramuscular immunomodulatory agent, composed of sodium oxodihydroacridinylacetate)
- Prostaglandins (e.g., bimatoprost, latanoprost, and prostaglandin E2)
- Split thickness skin grafting
- Tars
- Topical minoxidil
- Topical phenytoin gel
- Topical pseudocatalase
• Tumor necrosis factor-alpha agents (e.g., adalimumab, etanercept, and infliximab)
• Vitamin D analogs (e.g., calcitriol and paricalcitol).

Background

Vitiligo is an acquired pigmentary disorder of skin and mucous membranes, manifesting itself by expanding depigmented lesions. While the cause is not well understood, the observed variation in clinical manifestations of the condition has suggested several possible etiologies, including association with other medical conditions. The 3 prevailing theories of the pathogenesis of vitiligo include an immune hypothesis, a neural-mediated hypothesis, and a “self-destruct” hypothesis. These 3, plus newer hypotheses suggesting that vitiligo may be due to a melanocyte growth factor deficiency or to an abnormal melatonin receptor on melanocytes, have not been definitively proven, and it is likely that the loss of epidermal and follicular melanocytes in vitiligo may be the result of several different pathogenic mechanisms.

Psoralen photochemotherapy (psoralen and ultraviolet light A or PUVA) is appropriate for properly selected patients with vitiligo. The treatment involves taking oral psoralen or applying it topically followed by carefully timed exposure to UVA. Repigmentation may begin after 15 to 25 treatments. Approximately 50% of patients will develop repigmentation after 150 to 200 PUVA treatments over 12 to 24 months. The response is slow and repigmentation may not be complete. Response to PUVA is unlikely to occur if follicular pigmentation has not appeared after 3 months of PUVA therapy. Dark-skinned patients respond better than fair skin patients do; the latter are unlikely to benefit from PUVA unless there is marked disfigurement. Most patients who respond do not develop new areas of pigment loss; furthermore, maintenance with PUVA therapy is not necessary.
Children under age 10 are generally not treated with oral phototherapy; instead, a mild topical corticosteroid cream is often prescribed. A stronger topical corticosteroid cream can be prescribed for adults. Patients must apply the cream (e.g., triamcinolone 0.1 %, desonide 0.05 %) once-daily to the white patches on their skin for at least 3 to 4 months before seeing any results. Systemic corticosteroids can stop the progression of vitiligo for some patients, but may also produce unacceptable side effects. Oral mini-pulse therapy with 5 mg betamethasone/dexamethasone may stop the progression and induce spontaneous repigmentation in some vitiligo patients.

A number of recently published studies have demonstrated that narrow-band UVB is an effective treatment for vitiligo, and compares favorably to UVA and psoralens (e.g., Westerhof, 1997; Njoo et al, 2000; Scherschun et al, 2001). Unlike PUVA, narrow-band UVB does not involve the use of sensitizing agents. Narrow-band UVB is typically administered 2 to 3 times per week for several months. However, there is a lack of evidence regarding the safety and effectiveness of home narrow-band UVB phototherapy for the treatment of vitiligo.

In a randomized controlled study, Ada et al (2005) concluded that narrow-band UVB phototherapy is effective in treating vitiligo, and the addition of topical calcipotriol does not improve treatment outcome.

In a double-blind randomized study, Yones et al (2007) compared the effectiveness of oral PUVA with that of narrowband-UVB (NB-UVB) phototherapy in patients with non-segmental vitiligo. A total of 56 patients received twice-weekly therapy with PUVA or NB-UVB. The change in body surface area affected by vitiligo and the color match of repigmented skin compared with unaffected skin were assessed after 48 sessions of therapy, at the end of the therapy course, and 12 months after the end of therapy. The results in the 25 patients each in the PUVA and NB-UVB groups who began therapy were analyzed. The median number of treatments was 47 in
the PUVA-treated group and 97 in the NB-UVB-treated group (p = 0.03); this difference was probably due to differences in effectiveness and adverse effects between the 2 modalities, such that patients in the NB-UVB group wanted a longer course of treatment. At the end of therapy, 16 (64 %) of 25 patients in the NB-UVB group showed greater than 50 % improvement in body surface area affected compared with 9 (36 %) of 25 patients in the PUVA group. The color match of the repigmented skin was excellent in all patients in the NB-UVB group but in only 11 (44 %) of those in the PUVA group (p < 0.001). In patients who completed 48 sessions, the improvement in body surface area affected by vitiligo was greater with NB-UVB therapy than with PUVA therapy (p = 0.007). Twelve months after the cessation of therapy, the superiority of NB-UVB tended to be maintained. The authors concluded that in the treatment of non-segmental vitiligo, NB-UVB therapy is superior to oral PUVA therapy.

In a randomized, investigator-blinded and half-side comparison study, Casacci and colleagues (2007) compared the effectiveness of NB-UVB phototherapy and 308-nm monochromatic excimer light (MEL) in patients with vitiligo. A total of 21 subjects with symmetrical vitiligo lesions were enrolled in this study. Vitiligo lesions on one body side were treated twice-weekly for 6 months with 308-nm MEL, while NB-UVB phototherapy was used to treat lesions on the opposite side. At the end of the study, 6 lesions (37.5 %) treated with 308-nm MEL and only 1 lesion (6 %) treated with NB-UVB achieved an excellent repigmentation (score 4) while 4 lesions (25 %) treated with 308-nm MEL and 5 lesions (31 %) treated with NB-UVB showed a good repigmentation (score 3). The authors concluded that it appears that 308-nm MEL is more effective than NB-UVB in treating vitiligo lesions and it induces repigmentation more rapidly.

Several clinical studies have demonstrated that the Xenon-Chloride excimer laser is effective in repigmentation of vitiligo patches (Hadi et al, 2004; Choi et al, 2004; Esposito et al,
The excimer laser may be especially useful in treatment of localized vitiligo that is refractory to topical corticosteroids. Treatments are typically administered twice weekly and up to 60 treatments may generally be medically necessary. Recent studies have also suggested that combination treatment with excimer laser and topical methoxypsoralen resulted in better repigmentation than excimer laser alone. However, due to the small sample sizes in these studies, their findings need to be validated by additional studies (Grimes, 2005).

Transplantation of autologous pigment cells is considered experimental and investigational for the treatment of vitiligo because of a lack of adequate clinical evidence of effectiveness from randomized controlled clinical trials.

van Geel and colleagues (2006) investigated the effectiveness of non-cultured epidermal cell transplantation in treating stabilized vitiligo using objective and subjective evaluation methods. Non-cultured autologous melanocytes and keratinocytes were grafted in a hyaluronic-acid-enriched suspension on superficially laser-abraded vitiligo lesions in 40 patients with refractory stable vitiligo (30 with generalized and 10 with localized vitiligo). The repigmentation was evaluated 3 to 12 months after grafting using a digital image analysis system. Furthermore, the treatment was evaluated from patients' point of view with the DLQI (Dermatology Life Quality Index) and a global assessment. The mean percentage of repigmentation, evaluated at the last follow-up visit, was 72% (median of 84%), and a repigmentation of greater than or equal to 70% was observed in 62% of patients. The best results were achieved in the neck and the pre-sternal region. A subjective evaluation was performed in 50% of the subjects. The mean DLQI score at inclusion (6.95, SD = 6.68, n = 20) was significantly lowered after treatment (p = 0.013, mean 3.85, SD = 4.13, n = 20). The patients were satisfied with the achieved result, and they found it worthwhile to
undergo the treatment and would choose it again. The authors concluded that according to both subjective and objective evaluation methods, non-cultured epidermal cell transplantation is promising in patients with stable vitiligo.

In a randomized, double-blind clinical trial, Rodríguez-Martín and colleagues (2009) assessed the safety and effectiveness of tacalcitol (a vitamin D analog) ointment plus sunlight exposure in the treatment of non-segmental vitiligo. A total of 80 patients participated in this study. Effectiveness was assessed by quantification of the lesional re-pigmentation area at the end of the study compared with the baseline. Tacalcitol (n = 40) or matching placebo ointment (n = 40) was applied once-daily at night. Daily exposure to sunlight for 30 mins was performed. Treatment was continued for 4 months. The response of the lesions was clinically verified every 2 weeks by a "blinded" medical investigator. All adverse effects were recorded. Over 16 weeks, 64 patients completed the study requirements. There was no significant difference in the re-pigmentation response at the 16-week time point between the vehicle plus sunlight exposure and the tacalcitol plus sunlight exposure groups. No reduction in the size of the lesions greater than 25 % was observed in the tacalcitol-treated patients. No serious adverse effects were observed. The authors concluded that the combination of tacalcitol with heliotherapy has no additional advantages compared with heliotherapy alone.

In a Cochrane review on interventions for vitiligo, Whitton et al (2010) stated that new interventions include MEL, polypodium leucotomos, melanocyte transplantation, oral anti-oxidants, Chinese zengse pill, and pimecrolimus. These investigators analyzed the data from 28 studies that met their outcome criteria of improvement in quality of life and greater than 75 % repigmentation. A total of 15 analyses from studies comparing various interventions showed a statistically significant difference between the proportions of participants achieving more than 75 % repigmentation. The majority of
analyses showing statistically significant differences were from studies that assessed combination interventions that generally included some form of light treatment. Topical preparations, in particular corticosteroids, reported most adverse effects. However, in the combination studies it was difficult to ascertain which treatment caused these effects. None of the studies was able to demonstrate long-term benefits. Very few studies were conducted on children or included segmental vitiligo. These researchers found 1 study of psychological interventions and none evaluating micropigmentation, depigmentation, or cosmetic camouflage. The authors concluded that this review has found some evidence from individual studies to support existing therapies for vitiligo, but the usefulness of the findings is limited by the different designs and outcome measurements and lack of quality of life measures. There is a need for follow-up studies to assess permanence of repigmentation as well as high quality randomized trials using standardized measures and which also address quality of life.

Alghamdi and colleagues (2012) stated that although the exact pathogenesis of vitiligo is not fully understood, it appears to be an autoimmune disease. It is hypothesized that tumor necrosis factor-alpha (TNF-alpha) plays an important role in vitiligo. Tumor necrosis factor-alpha can destroy melanocytes through the induction of various apoptotic pathways. In addition, TNF-alpha can inhibit melanocyte stem cell differentiation. These researchers evaluated the safety and effectiveness of treating vitiligo patients with anti-TNF-alpha agents. A total of 6 patients were recruited. All patients had widespread non-segmental vitiligo. Biologics, including infliximab, etanercept, and adalimumab, were given according to treatment regimens used for psoriasis. Photographs were taken at the initial visit, every 2 months during the therapy and then 6 months after therapy completion. All patients completed the treatment; 2 patients were treated with infliximab, 2 with etanercept, and 2 with adalimumab. All of the biologics were well-tolerated throughout the treatment...
period, and none of the patients reported any significant adverse events. Digital images were compared before, during and after treatment. Repigmentation of the vitiliginous areas was not observed in any of the patients. Vitiligo worsened in 1 patient who was treated with infliximab and developed a psoriasiform rash. However, the remaining patients did not develop any new depigmented patches during treatment or at the 6-month follow-up; vitiligo was considered stable in these 5 patients. The authors concluded that although the anti-TNF-alpha agents were well-tolerated in all 6 vitiligo patients, efficacy was not observed. They stated that further evaluation with larger studies may be required.

In a pilot study, Dayel et al (2013) evaluated the safety and effectiveness of alefacept in the treatment of vitiligo. After providing informed written consent, 4 adult patients with widespread vitiligo (covering a body surface area greater than or equal to 5 %) were treated with weekly intra-muscular injections of 15 mg alefacept for 12 weeks. All patients were monitored clinically, by laboratory investigation, and by digital image analysis. All patients were followed-up with for 24 weeks. All patients tolerated alefacept well, without any adverse events. None of the patients showed any repigmentation. However, 1 patient developed new depigmented patches during treatment with alefacept. The authors concluded that alefacept as a monotherapy for vitiligo treatment did not result in any patient improvement, and further evaluation in larger studies may be required.

Wong and Lin (2013) stated that topical calcineurin inhibitors (e.g., pimecrolimus and tacrolimus) are indicated for the treatment of atopic dermatitis, but they have been studied in many off-label uses. These investigators reviewed the English language literature to define their roles in treatment of vitiligo. Double-blind studies showed that tacrolimus 0.1 % ointment combined with excimer laser is superior to placebo, especially for UV-resistant areas, such as bony prominences of the extremities. When used alone, tacrolimus 0.1 % ointment is
almost as effective as clobetasol propionate 0.05 % ointment. Other studies suggested it can also be effective for facial lesions. Double-blind studies showed that pimecrolimus 1 % cream combined with narrow band UVB is superior to placebo, especially for facial lesions. Moreover, the authors concluded that additional studies would further clarify the role of topical calcineurin inhibitors in vitiligo.

An UpToDate review on “Vitiligo” (Goldstein and Goldstein, 2013) states that “Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) may be an effective therapy for vitiligo; however, most of the evidence of their use comes from small case series and uncontrolled trials…. In 2005, the United States Food and Drug Administration (FDA) issued an alert about a possible link between topical tacrolimus and pimecrolimus and cases of lymphoma and skin cancer in children and adults, and in 2006 placed a "black box" warning on the prescribing information for these medications. No definite causal relationship has been established; however, the FDA recommended that these agents only be used as second-line agents for atopic dermatitis. If these agents are used for the treatment of vitiligo, it would be reasonable to follow the additional safety recommendations made by the FDA for their use in atopic dermatitis”.

Grimes et al (2013) noted that many recent studies have demonstrated defects in the melanocortin system in patients with vitiligo, including decreased circulating and lesional skin levels of α-melanocyte stimulating hormone (α-MSH). Afamelanotide is a potent and longer-lasting synthetic analog of naturally occurring α-MSH. These investigators described the preliminary results of 4 patients with generalized vitiligo who developed re-pigmentation using afamelanotide in combination with narrowband UV-B (NB-UV-B) phototherapy. Patients were treated 3 times weekly with NB-UV-B and starting in the 2nd month received a series of 4 monthly implants containing 16 mg of afamelanotide. Afamelanotide induced faster and deeper re-pigmentation in each case. All
patients experienced follicular and confluent areas of re-pigmentation within 2 days to 4 weeks after the initial implant, which progressed significantly throughout treatment. All patients experienced diffuse hyper-pigmentation. The authors proposed that afamelanotide represents a novel and potentially effective treatment for vitiligo. The combined therapy of NB-UV-B and afamelanotide appears to promote melanoblast differentiation, proliferation, and eumelanogenesis. They stated that further studies are necessary to confirm these observations.

Mulekar and Isedeh (2013) evaluated the evidence for the safety, effectiveness and applicability of the various surgical methods in the treatment of vitiligo. For this systematic review of vitiligo surgical therapies, the searches included: PubMed, MEDLINE and Cochrane databases. These investigators reviewed studies reporting on autologous mini-punching grafting, blister roof grafting (suction epidermal blister grafting), cultured and non-cultured cellular melanocyte keratinocyte transfer, split thickness skin grafting (STSG). While all methods vary in their re-pigmentation outcomes, STSG is found to have the highest re-pigmentation success rate. Overall, post-operative complications included milia, scarring, cobblestone appearance or hyper-pigmentation of treated areas. The authors concluded that this review highlighted the need for more randomized controlled trials in this field, underpinned by a more standardized objective approach to the assessment of re-pigmentation following surgical interventions.

Al Jasser (2013) reported the benefit of autologous non-cultured melanocyte-keratinocyte transplantation (MKT) in patients with vitiligo-associated leukotrichia. All 4 patients showed significant re-pigmentation in vitiligo-associated leukotrichia after MKT. The authors concluded that melanocyte-keratinocyte transplantation may represent a good therapeutic option for the re-pigmentation of vitiligo-associated
leukotrichia. Moreover, they stated that larger prospective studies are needed to determine the true response rate and mechanism of re-pigmentation.

In a pilot study, Ruiz-Arguelles et al (2013) reported the findings of treatment of vitiligo with a chimeric monoclonal antibody to CD20. Five patients with active disseminated vitiligo were given 1 g of a chimeric (murine/human) monoclonal antibody to CD20 in a single intravenous infusion and followed-up for 6 months. Three of the patients showed an overt clinical and histological improvement of the disease, 1 presented slight improvement and the remaining patient showed no changes. Improvement was neither associated with changes in laboratory parameters nor to a specific human leucocyte antigen D-related (HLA-DR) phenotype. The authors concluded that these preliminary results were encouraging, and further clinical trials should be undertaken.

Furthermore, an UpToDate review on “Vitiligo” (Goldstein and Goldstein, 2014) does not mention the use of chimeric monoclonal antibody to CD20/rituximab as a therapeutic option.

The British Association of Dermatologists' guideline on “The diagnosis and management of vitiligo” (Gawkrodger et al, 2008), which have been cited by the American Academy of Dermatology, stated that topical pimecrolimus or tacrolimus should be considered as alternatives to the use of a highly potent topical steroid in view of their better short-term safety profile. Furthermore, the European Dermatology Forum guideline on “Vitiligo” also recommended the use of calcineurin inhibitors as first-line therapy for segmental vitiligo or limited non-segmental Vitiligo (less than 2 to 3 % of body surface).

Eleftheriadou and colleagues (2014) noted that hand-held NB-UVB units are light-weight devices that may overcome the need to treat vitiligo in hospital-based phototherapy cabinets, allowing early treatment at home that may enhance the
likelihood of successful re-pigmentation. The pilot Hi-Light trial examined the feasibility of conducting a large multi-center, randomized controlled trial (RCT) on the use of such devices by exploring recruitment, adherence, acceptability, and patient education. This was a feasibility, double-blind, multi-center, parallel group RCT of hand-held NB-UVB phototherapy for the treatment of vitiligo at home. The overall duration of the trial was 7 months; 3 months recruitment and 4 months treatment. Participants were randomly allocated to active or placebo groups (2:1 ratio). The primary outcome measure was the proportion of eligible participants who were willing to be randomized. The secondary outcomes included proportion of participants expressing interest in the trial and fulfilling eligibility criteria, withdrawal rates and missing data, proportion of participants adhering to and satisfied with the treatment, and incidence of NB-UVB short-term adverse events. A total of 83% (45/54) of vitiligo patients who expressed interest in the trial were willing to be randomized. Due to time and financial constraints, only 29/45 potential participants were booked to attend a baseline hospital visit. All 29 (100%) potential participants were confirmed as being eligible and were subsequently randomized. Willingness to participate in the study for General Practice (family physicians) surgeries and hospitals were 40% and 79%, respectively; 86% (25/29) of patients adhered to the treatment and 65% (7/11) of patients in the active group had some degree of re-pigmentation. Only 1 patient in the active group reported erythema grade 3 (3%). Both devices (Dermfix 1000 NB-UVB and Waldmann NB-UVB 109) were acceptable to participants. The authors concluded that hand-held NB-UVB devices need evaluation in a large, pragmatic RCT. This pilot trial has explored many of the uncertainties that need to be overcome before embarking on a full scale trial, including the development of a comprehensive training package and treatment protocol. The study has shown strong willingness of participants to be randomized, very good treatment adherence...
and re-pigmentation rates, and provided evidence of feasibility for a definitive trial. This trial was not intended as an efficacy trial.

**Combination of Topical Calcineurin Inhibitors and Phototherapy for the Treatment of Vitiligo**

In a meta-analysis, Dang et al (2016) examined the effect of topical calcineurin inhibitors as monotherapy or combined with phototherapy for vitiligo treatment. These investigators searched the MEDLINE, Embase, and Cochrane central register of controlled trials databases for articles published prior to September 2014. A total of 13 studies were included in the meta-analysis. After pooling the trials, these researchers concluded that calcineurin inhibitors showed a better therapeutic effect on vitiligo than placebo, according to lesion report (risk ratio [RR] = 2.62, 95% confidence interval [CI]: 1.39 to 4.93, p = 0.003) and patient report (RR = 1.42, 95% CI: 0.87 to 2.31, p = 0.157). Subgroup analysis was performed to examine if the combination with phototherapy was a source of heterogeneity. The trial sequence analysis indicated that the results of combined therapy by lesion report were reliable and conclusive. However, in the patient report trials, the frequency of lesions on the hand and foot was higher, and the effect of combined therapy was still non-significant. The authors concluded that calcineurin inhibitors showed a better therapeutic effect than placebo in the treatment of vitiligo with phototherapy. However, the typical UV-resistant sites (i.e., hand and foot) were still difficult to cure even with combined therapy. Moreover, they stated that because of concerns about photo-carcinogenesis, the clinical application of combined therapy should be explored with caution.

**Gene Polymorphisms Testing for Early Detection of Vitiligo**
Lu and co-workers (2014) evaluated the association of the catalase (CAT) 389 C/T polymorphism with susceptibility to vitiligo. These investigators undertook a literature search and included the relevant studies passing the selection criteria. After the relevant data were extracted from each study, they statistically analyzed the strength of association between the CAT gene and vitiligo risk. A total of 7 relevant studies were identified, comprising 1,531 patients with vitiligo and 1,608 controls. The genotype distribution in the controls of all studies complied with Hardy-Weinberg equilibrium. After pooling all studies, the results indicated that the 389 C/T polymorphisms in CAT were not associated with the risk of vitiligo in Asians and Turks; however the CT genotype might be a genetic risk factor for susceptibility to vitiligo (odds ratio (OR) = 1.77, 95 % CI: 1.30 to 2.43, p < 0.001) and the CC genotype might decrease the risk of vitiligo (OR = 0.63, 95 % CI: 0.47 to 0.86, p < 0.01) in western Europeans. The authors concluded that the 389 C/T polymorphisms in the CAT gene may be associated with vitiligo in western Europeans. They stated that further studies with larger sample sizes are needed to confirm these findings.

He and associates (2015) noted that the CAT T/C at codon 389 in the exon 9 polymorphism has been implicated in susceptibility to vitiligo but a large number of studies have reported inconclusive results. These researchers assessed the association between the catalase gene polymorphism (389C>T) and the risk of vitiligo. These investigators performed a meta-analysis to analyze the association between 389C>T and vitiligo risk. A total of 8 case-control studies with 2,923 cases and 4,237 controls were included in the meta-analysis. The results indicated that there was no association between this polymorphism and vitiligo (TT + CT versus CC: OR = 1.08, 95 % CI: 0.98 to 1.20, p = 0.11, T versus C: OR=1.07, 95 % CI:0.99 to 1.16, p = 0.092). In a subgroup analysis by ethnicity, no significant association between the CAT gene 389C>T polymorphism and vitiligo susceptibility was found in Caucasians (TT + CT versus CC: OR = 1.15, 95% CI=
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0.98-1.35, \( P = 0.08 \); \( T \text{ versus } C \): \( \text{OR} = 1.07 \), 95% CI = 0.97-1.19, \( P = 0.173 \) and Asians \( (TT + CT \text{ versus } CC) \): \( \text{OR} = 1.12 \), 95% CI: 0.93 to 1.34, \( p = 0.23 \); \( T \text{ versus } C \): \( \text{OR} = 1.07 \), 95% CI: 0.94 to 1.21, \( p = 0.321 \). The authors concluded that these findings suggested that 389C>T may not contribute to vitiligo susceptibility. However, larger primary studies with the consideration of gene-environment and gene-gene interactions are still needed to further evaluate the interaction of CAT gene polymorphism with vitiligo susceptibility.

In a meta-analysis, Li and colleagues (2015) evaluated the association between 2 common polymorphisms (ApaI and BsmI) in the VDR gene and the susceptibility to vitiligo. The PubMed, Cochrane Library and China National Knowledge Infrastructure (CNKI) databases were searched; and OR with 95% CI was calculated. The strength of association and vitiligo risk was assessed under 5 genetic models: (i) allele, (ii) dominant, (iii) recessive, (iv) homozygous, and (v) heterozygous. A total of 6 relevant studies were identified, including 5 studies that assessed the ApaI polymorphism and 4 the BsmI polymorphism (some overlapped). The meta-analysis results indicated that either the ApaI or the BsmI gene polymorphism may increase the risk of vitiligo in East Asian populations \( (aa + Aa \text{ versus } AA) \): \( \text{OR} = 1.40 \), 95% CI: 1.01 to 1.96, \( p < 0.05 \); \( bb \text{ versus } Bb + BB \): \( \text{OR} = 1.32 \), 95% CI: 1.09 to 1.59, \( p < 0.01 \). No publication bias was detected in this meta-analysis. The authors concluded that the current meta-analysis suggested that the ApaI a allele or BsmI bb genotype are associated with the risk of vitiligo in East Asian populations. Thus, these polymorphisms could be potential biomarkers for early detection of vitiligo.

Cytotoxic T-Lymphocyte Antigen (CTLA)-4+49A/G Polymorphism Testing

Liang et al (2015) noted that cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a critical negative regulator of T-cell activation and proliferation. Several studies have assessed the association
between CTLA-4+49A/G polymorphism and psoriasis and vitiligo, but the results are inconsistent. In a meta-analysis, these researchers examined the association between CTLA-4+49A/G polymorphism and psoriasis and vitiligo susceptibility. The PubMed, Embase, and China National Knowledge Infrastructure (CNKI) databases were searched according to predefined criteria for all relevant studies published prior to July 3, 2014. Odds ratios with 95% CIs, and heterogeneity and publication bias tests were performed to estimate the strength of the association. A total of 14 studies comprising 6 on psoriasis (700 cases, 781 controls) and 8 on vitiligo (1,514 cases, 2,049 controls) were included. Overall, no significant association was detected between CTLA-4+49A/G polymorphism and psoriasis. There was still no significant relationship when the studies were limited to ethnicity (Asian and Caucasian), HWE or heterogeneity, except the limitation to heterogeneity in the dominant (OR = 0.69, 95% CI: 0.51 to 0.93, I(2) = 0.0 %) and additive (OR = 0.69, 95% CI: 0.48 to 0.98, I(2) = 0.0 %) models, and the limitation to both heterogeneity and HWE in the dominant model (OR = 0.68, 95% CI: 0.48 to 0.98, I(2) = 0.0 %). Both overall and subgroup analyses based on ethnicity, genotype frequencies, and heterogeneity also failed to demonstrate an association between CTLA-4+49A/G polymorphism and vitiligo. The authors concluded that CTLA-4+49A/G polymorphism may not contribute to psoriasis and vitiligo susceptibility, but further well-designed studies with large sample size are needed to confirm this conclusion.

TNF-Alpha-308G/A Polymorphism Testing

Nie and colleagues (2015) noted that several case-control studies have been conducted to investigate the association between the TNF-alpha (TNF-α)-308G/A polymorphism and vitiligo risk. However, the results of these studies are inconsistent; therefore, these researchers attempted to comprehensively evaluate the association between TNF-α-308G/A polymorphism and vitiligo risk via a meta-analysis.
Studies reporting the association between TNF-α-308G/A polymorphism and vitiligo risk were retrieved from PubMed and EmBase databases. Data were extracted from these studies and the pooled ORs with 95% (CIs were calculated to assess the association. A total of 6 case-control studies including 1,391 vitiligo cases and 2,455 control subjects were included in this meta-analysis. The overall results showed the lack of a significant difference in TNF-α-308G/A genotype distribution between the patients and controls when the G allele and GG, GG + GA, GG, and GG genotypes were compared against the A allele and the GA + AA, AA, AA, and GA genotypes, respectively (ORs = 0.65, 0.53, 0.63, 0.41, 0.55; 95% CI: 0.35 to 1.23, 0.24 to 1.18, 0.10 to 4.09, 0.08 to 1.97, 0.25 to 1.21; p = 0.188, 0.121, 0.627, 0.264, 0.135, respectively). The authors concluded that the findings of this meta-analysis suggested that the TNF-α-308G/A polymorphism may not be associated with vitiligo risk. They stated that as few studies are available in this field and current evidence remains limited, these results must be corroborated with well-designed and larger studies in the future.

Human Leukocyte Antigen-A Polymorphism Testing

Li and colleagues (2016) evaluated the association between vitiligo and human leukocyte antigen- (HLA-) A. Methods. PubMed, Embase, Web of Science, Chinese National Knowledge Infrastructure, and reference lists were searched for relevant original articles. Results. Nineteen case-control studies comprising 3042 patients and 5614 controls were included, in which 33 HLA-A alleles were reported. Overall, three alleles (HLA-A⁎02, A⁎33, and Aw⁎31) were significantly associated with increased risk of vitiligo, two (HLA-A⁎09 and Aw⁎19) were associated with decreased risk, and the remaining 28 were unassociated. Twelve alleles, seven alleles, and 19 alleles were common to three ethnicities, both types of vitiligo, and both typing methods, respectively. In the subgroup analysis by ethnicity and typing methods, the association of six alleles and five alleles was inconsistent in
three populations and both typing methods, respectively. In the subgroup analysis by clinical type, the association of all seven alleles was consistent in both types of vitiligo. Conclusion. The meta-analysis suggests that HLA-A*02, A*33, and Aw*31 are associated with increased risk of vitiligo, while HLA-A*09 and Aw*19 are associated with decreased risk of vitiligo. The association of some alleles varies in terms of ethnicity and typing methods.

This study has some limitations. First, the meta-analysis only included published studies. Second, vitiligo may be influenced by not only genetic factors but also environmental factors. The results of the meta-analysis should be interpreted cautiously owing to the lack of available data regarding vitiligo development and its relationship with genetic and environmental factors. Further studies may assess the possible gene-environment interactions in the association. Third, the relatively small samples of some HLA-A alleles limited the statistical power. Finally, we were not able to perform subgroup for each HLA-A allele due to the limited number of eligible studies, which might have affected the results. Therefore, more studies with larger sample sizes focusing on each HLA-A allele are needed to confirm these findings. Despite the limitations listed above, this study still has some strength. To the best of our knowledge, this is the first meta-analysis evaluating the association between vitiligo and a number of HLA-A alleles.

In summary, this meta-analysis suggests that HLA-A*02, A*33, and Aw*31 are associated with increased risk of vitiligo, while HLA-A*09 and Aw*19 are associated with decreased risk of vitiligo. Moreover, the association of some alleles varies in terms of ethnicity and typing methods. However, further well-designed studies with larger sample sizes are still needed to confirm our findings.
Protein Tyrosine Phosphatase, Non-Receptor Type 22 +1858C→T Polymorphism Testing

Agarwal and Changotra (2017) stated that protein tyrosine phosphatase, non-receptor type 22 gene, which translates to lymphoid tyrosine phosphatase, is considered to be a susceptibility gene marker associated with several autoimmune diseases. Several studies have demonstrated the association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism with vitiligo. However, these studies showed conflicting results. Meta-analysis of the same was conducted earlier that included fewer number of publications in their study. These researchers performed a meta-analysis of a total of 7 studies consisting of 2,094 cases and 3,613 controls to evaluate the possible association of protein tyrosine phosphatase, non-receptor type 22 +1858C>T polymorphism with vitiligo susceptibility. They conducted a literature search in PubMed, Google Scholar and Dogpile for all published paper on protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism and vitiligo risk till June 2016. Data analysis was performed by RevMan 5.3 and comprehensive meta-analysis v3.0 software. Meta-analysis showed an overall significant association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism with vitiligo in all models (allelic model [T versus C]: OR = 1.50, 95 % CI: 1.32 to 1.71, p < 0.001; dominant model [TT + CT versus CC]: OR = 1.61, 95 % CI: 1.16 to 2.24, p = 0.004; recessive model [TT versus CT + CC]: OR = 4.82, 95 % CI: 1.11 to 20.92, p = 0.04; homozygous model [TT versus CC]: OR = 5.34, 95 % CI: 1.23 to 23.24, p = 0.03; co-dominant model [CT versus CC]: OR = 1.52, 95 % CI: 1.09 to 2.13, p = 0.01). No publication bias was detected in the funnel plot study. The authors noted that stratifying data by ethnicity showed an association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T with vitiligo in European population (OR = 1.53, 95 % CI: 1.34 to 1.75, p < 0.001); but not in Asian population (OR = 0.59, 95 % CI: 0.26 to 1.32, p = 0.2). The authors concluded that protein tyrosine
phosphatase, non-receptor type 22 +1858 T allele predisposed European individuals to vitiligo. The major drawbacks of this meta-analysis were that as a consequence of ethnic-based studies, these investigators were unable to satisfy data by gender or vitiligo-type.

NLRP1 Gene Polymorphisms Testing for Susceptibility to Vitiligo and Associated Autoimmune Diseases

Li and co-workers (2017) stated that genetic variants are linked to vitiligo and associated autoimmune diseases. In a meta-analysis, these investigators evaluated the effects of the rs12150220, rs2670660, and rs6502867 polymorphisms within the human NLR Family Pyrin Domain Containing 1 (NLRP1) gene. They initially identified 1,306 candidate articles through literature searches of PubMed, WOS, Embase, CNKI, WANFANGI, Ovid, Scopus, and Cochrane in July 2017. After strict screening, these researchers included 19 eligible case-control studies, and analyzed the data using Stata/SE 12.0 software. No difference between vitiligo cases and controls was detected for NLRP1 rs12150220, rs2670660, or rs6502867 under most genetic models \( P_{\text{association}} (\text{p value of association test}) > 0.05 \). With regard to vitiligo-associated autoimmune diseases, like Addison's disease, type 1 diabetes mellitus (T1DM), or systemic lupus erythematosus (SLE), a decreased risk was detected for rs12150220 in the Caucasian subgroup under all models \( P_{\text{association}} < 0.05, \text{OR} < 1 \). No relationships were observed for other polymorphisms, including rs2670660, rs6502867, and the "A-A, G-T, G-A, A-T" haplotypes of rs2670660/rs12150220 \( P_{\text{association}} > 0.05 \).

This meta-analysis demonstrated that within the Caucasian population, the NLRP1 rs12150220 polymorphism may correlate with a decreased risk of vitiligo-associated autoimmune diseases, especially autoimmune Addison's disease, T1DM, or SLE. The authors concluded that they identified a potential genetic relationship in the Caucasian population between the NLRP1 rs12150220 polymorphism and a decreased susceptibility to autoimmune diseases,
especially autoimmune Addison's disease, T1DM, or SLE. These autoimmune diseases were all tightly associated with vitiligo. However, these researchers did not observe a strong association between NLRP1 rs12150220, rs2670660, or rs6502867 and vitiligo risk, according to the currently very limited data. Similarly, rs2670660 and rs6502867 polymorphisms and rs2670660/rs12150220 haplotypes (A-A, G-T, G-A, A-T) within NLRP1 appeared to have no effect on the risk of vitiligo-associated autoimmune diseases. They stated that given the fact of insufficient statistical power as stated above, more data are needed to confirm these statements, and further determine the role of NLRP1 SNPs in the presence of vitiligo, or vitiligo together with autoimmune diseases.

Blist er Roof Grafting

Janowska and colleagues (2016) stated that vitiligo is a multifactorial acquired dermatosis characterized by achromic or hypochromic macules and by the absence of functioning melanocytes. Treatment depends on the extent of the affected areas and on disease activity. Surgical techniques have proven to be effective in stable cases but can be time-consuming and, in some cases, aesthetically unsatisfying or painful for the patients. These researchers evaluated the clinical safety and effectiveness of a new automatic epidermal skin harvesting device in patients with stable localized vitiligo over a minimum 12-month period. This new system (CELLUTOME Epidermal Harvesting System, KCI, an A CELITY Company, San Antonio, TX) is a commercially available epidermal skin harvesting system that can be used without local anesthesia or other pre-treatments and has been shown to have low rates of donor site morbidity. Epidermal skin grafts can be used in patients with acute and hard to heal chronic wounds, burns and stable vitiligo. The use of advanced therapies may improve the quality of life, have cost benefits and accelerate re-pigmentation of patients with vitiligo. In a pilot study, the authors stated that this system
was seen to be a safe and effective means of harvesting epidermal micrografts containing melanocytes for use in patients with stable vitiligo unresponsive to standard therapies.

Cai and associates (2016) stated that epidermal grafting has several advantages over full-thickness or split-thickness grafts in the treatment of complex non-healing wounds. These include the low risk of donor site complications, minimal patient discomfort, and abstention from the operating room. Traditionally, the lack of reliable epidermal harvesting techniques has limited its clinical utilization. The development of an automated suction blister epidermal graft (SBEG) harvesting device may facilitate clinical utilization of this technique. These researchers presented a case series of multi-morbid patients who were poor surgical candidates and were treated with this technique. A retrospective review of all patients treated with CelluTome Epidermal Harvesting System (KCI, an Acelity company, San Antonio, TX) prior to May 2016 at the authors’ institution was conducted. A total of 12 patients underwent 14 epidermal grafting procedures. Multiple co-morbidities were identified, including smoking (33%), immunosuppression by immunotherapy or steroids (25%), chronic venous insufficiency (25%), diabetes mellitus (25%), malignancy (25%), poly-substance abuse (17%), HIV/AIDS (17%), and peripheral artery disease (8%). Among the 2 acute wounds (less than or equal to 3 months) and 10 chronic wounds, the average wound size was 49.1 cm² (± 77.6 cm²) and the median wound duration was 5.7 months (interquartile range [IQR]: 4.1 to 15.8 months) before SBEG was attempted. These complex wounds had failed prior therapies, such as local wound care (100%), incision and drainage (58%), vacuum-assisted closure (33%), split-thickness skin graft (16%), and hyperbaric oxygen therapy (8%). Following the procedure, all donor sites healed within 1 week; 3 patients were lost to follow-up. Of the remaining 9 patients, 4 patients had complete resolution of their wounds at a median follow-up of 13.1 weeks (IQR: 6.8 to 17.3 weeks). Among those with partial resolutions, the average wound size was 4.2 cm² (± 2.1
cm²) with an average wound reduction of 79% (± 23%). No donor or recipient site complications were observed. The authors concluded that the automated SBEG harvesting device was a safe and effective option for treating complex non-healing wounds in multi-morbid patients who may be poor surgical candidates.

The main drawback of this study was selection bias associated with the retrospective design. These investigators stated that in dealing with complex wounds, patient selection is an integral component of a successful outcome; patients with co-morbidities not suitable for the operating room, wound healing issues, and compliance concerns are poor candidates for traditional skin grafts. The autologous epidermal grafts effectively circumvent these problems and present an attractive alternative. The creation of an automated SBEG harvesting technique further simplified the procedure and minimized post-operative complications. The authors concluded that although this study has shown success in a variety of patients, identification of the ideal patient population may be of interest in follow-up studies.

Krishna and colleagues (2016) stated that vitiligo is a common pigmentary disorder of the skin with a great amount of social stigma attached to it. Although various medical modalities are available for the treatment of stable vitiligo, surgical modality remains the treatment of choice for stable and localized vitiligo. The surgical options range from simple punch grafting to the recent epidermal harvesting methods using a negative pressure unit. Although successful use of multiple methods of epidermal grafting has been reported, most of them are cumbersome and time-consuming. These researchers noted that new automated epidermal harvesting system now commercially available involves a tool that applies both heat and suction concurrently to normal skin to induce epidermal micrografts; it serves as a safe, quick and cost-effective method without anesthesia, with a very minimal downtime for healing and requires an optimal expertise. The duration of re-
pigmentation appeared to be faster and more uniform compared to other procedures. The authors concluded that more controlled studies are needed to prove the effectiveness of negative pressure epidermal harvesting in patients with stable vitiligo.

Janus Kinase Inhibitors for the Treatment of Vitiligo

Samadi and colleagues (2017) stated that janus kinase family (JAKs) has recently attracted the attention of many researchers, and several JAK inhibitor drugs have been developed targeting different members of the JAK family. Tofacitinib and ruxolitinib are FDA approved drugs in this family for rheumatoid arthritis and myeloproliferative diseases, respectively. Dysregulation of JAK/STAT pathway is also involved in many skin diseases, specifically inflammatory disorders. These investigators reviewed the JAK/STAT signaling pathway and its involvement in skin diseases; they also reviewed clinical studies of JAK inhibitors in field of dermatology, including psoriasis, atopic dermatitis, alopecia areata and vitiligo. The authors concluded that although the available evidence shows promising results, it is still too early to draw a firm conclusion about the place of these drugs in dermatological treatment.

Vu and colleagues (2017) noted that limited evidence exists for use of tofacitinib in atopic dermatitis (AD), alopecia areata (AA) and vitiligo. These investigators presented the case of a 44-year old white man with a lifelong history of AD presented with an acute exacerbation of the disease with secondary infection. He also had a 4-year history of AA (with previous alopecia totalis) and a 3-year history of non-segmental multifocal vitiligo. The AA and vitiligo had been persistent but stable during the preceding 3 months. The subject was treated with tofacitinib 5 mg twice-daily over 6 months. Concurrent treatment included prednisolone 5 mg daily and betamethasone dipropionate ointment. The authors concluded that their report added to the growing evidence to support use
of tofacitinib in AD, AA and perhaps vitiligo. Moreover, they stated that randomized controlled studies are needed to validate its efficacy in these dermatological conditions.

Prostaglandins for the Treatment of Vitiligo

An UpToDate review on “Vitiligo: Management and prognosis” (Grimes, 2017) lists afamelanotide (a potent and longer-lasting synthetic analog of naturally occurring alpha-melanocyte-stimulating hormone), prostaglandin E2, and bimatoprost (a synthetic analog of prostaglandin F2-alpha) as experimental therapies.

Dillon and colleagues (2017) stated that latanoprost (LT) is a prostaglandin F2-alpha analog that can induce skin pigmentation, a side effect discovered via its use in the treatment of glaucoma. It up-regulates tyrosinase and promotes melanocyte proliferation. A recent 22-patient, randomized, placebo-controlled trial comparing topical LT to NB-UVB and to the combination of the two, reported that the LT and NB-UVB combination was superior to NB-UVB therapy alone (62.5 versus 12.5 % with greater than 50 % repigmentation at 6 months, p < 0.05). Latanoprost alone yielded comparable results to NB-UVB (42.9 versus 28.6 % with greater than 50 % repigmentation at 6 months, p > 0.05) and superior outcomes to placebo (42.9 versus 0 % with greater than 50 % repigmentation at 6 months, p < 0.05). A Korean case series reported 3 patients with periorbital vitiligo who experienced 20, 50, and greater than 90 % repigmentation after 2 months of topical LT therapy. Likewise, a phase IV clinical trial in India investigating topical bimatoprost 0.03 % solution twice-daily observed 50 to 100 % repigmentation in 7 of 10 patients after 4 months. Results were first visible at 2 months, and patients with recalcitrant, focal vitiligo as well as those with disease duration less than 6 months tended to respond best. The authors stated that these promising results clearly warrant further investigation into LT’s safety and effectiveness for the treatment of vitiligo.
Jha and colleagues (2018) evaluated the efficacy of topical bimatoprost ophthalmic solution in stable facial vitiligo. A total of 8 cases of stable facial vitiligo were treated with bimatoprost 0.03 % ophthalmic solution once-daily for 12 weeks. Photographic records were taken at 2 weeks follow-up along with dermoscopic (Polarized, 10×) evaluation; 4 cases had excellent re-pigmentation, 2 cases had partial re-pigmentation and 2 cases had poor response. The authors concluded that bimatoprost appeared to be promising in treating stable vitiligo; but large-scale studies are needed.

Apremilast

Huff and Gottwald (2017) stated that psoriasis, alopecia areata, and vitiligo share a common pathway of autoimmunity, inflammatory signals, and cytokines present, although their pathogenesis is not completely understood. Apremilast is FDA-approved for psoriasis and psoriatic arthritis; it has also been shown to inhibit the development of alopecia areata. These researchers presented the case of a 52-year old woman with vitiligo for over 2 decades, and demonstrated the ability of apremilast to allow for re-pigmentation in this patient with chronic recalcitrant vitiligo in conjunction with initial systemic glucocorticoids. Moreover, they stated that additional clinical studies, ideally a randomized placebo-controlled trial, would be needed to prove that apremilast leads to re-pigmentation in vitiligo.

Topical Phenytoin Gel

Abdou and associates (2017) noted that there are many theories explaining vitiligo such as genetic, autoimmune, neural, free radicals, biochemical, intrinsic defect, melanocytorrhagy, and convergent theories. Phenytoin is a widely used anti-convulsant, which is used in cutaneous medicine for treatment of ulcers and epidermolysis bullosa. These researchers evaluated the effectiveness of topical phenytoin gel in the treatment of vitiligo patients and
explaining the underlying mechanism using immunohistochemistry for evaluation of HMB45, CD4, and CD8. Only 9 patients out of 28 experienced response to phenytoin in the form of dull, white color change and light brown color. Post-phenytoin treatment biopsies showed decreased density of inflammation, increased melanin and increased HMB45 positive cells together with an increased number of CD4-positive lymphocytes and decreased number of CD8-positive lymphocytes. These observations did not reach significant level (p > 0.05). A high percentage of CD4-positive lymphocytes was significantly associated with a long duration of vitiligo (p = 0.03) and segmental vitiligo type (p = 0.02). The current study applied phenytoin as 2% concentrated gel for 3 months, which was a relatively short duration without observed side effects throughout the period. The authors concluded that these findings indicated that topical phenytoin of low concentrations may have beneficial effects through immunomodulatory activity by affecting CD4 and CD8 counts and subsequently the ratio between them. They stated that further studies are recommended to combine phenytoin with other anti-vitiligo agents such as local corticosteroids or phototherapy to clarify if it could potentiate their effects.

Unconventional Treatments for Vitiligo

Gianfaldoni and colleagues (2018a) stated that despite the numerous therapies of proven efficacy available for vitiligo treatment, new unconventional drugs had been introduced for the correction of cutaneous disease in the last decades.

Capecitabine is an oral prodrug of fluorouracil, used in the treatment of metastatic colon and breast cancers. It has been reported that its use cause cutaneous hyperpigmentation. At the moment, more studies are needed to evaluate the potential use of the drug in the treatment of vitiligo.
Glutathione is a well-known antioxidant able to protect cellular components by oxidative stress damage. Recently, some studies underlined how its oral use as supplement may be useful in preventing cells photo-damage. However, the authors stated that more data are needed for its potential use in the treatment of vitiligo.

Melagenine is an alcohol extract of human placenta, which has been proposed for the topical treatment of vitiligo patients. Even if the exact mechanism of action is still unclear, it appeared to stimulate the melanoblast and melanocyte proliferation and the melanogenesis. It is usually applied twice-daily, alone or in association with ultraviolet radiation. Interestingly, a pilot study underlined the effectiveness of topical melagenine in combination with 20 minutes of infrared exposure twice-daily, in the re-pigmentation of scalp vitiligo.

Recently a new formulation of melagenine (Melagenina plus) has been formulated; it consists of a alcohol human placental extract with calcium. The drug is applied once-daily, and appeared to be effective in stimulating the re-pigmentation. No side effects had been described in the use of both Melagenine and Melagenine plus. However, no recent data are available on the use of melagenine in vitiligo.

Tars are oily, viscous material, consisting mainly of hydrocarbons, produced by the destructive distillation of organic substances such as wood, coal, or peat. Previously, they had been used for the topical treatment of psoriasis, both alone or in association to UVR. Because of their anti-inflammatory and immunosuppressive effects, tars had been also proposed for the treatment of vitiligo. However, they are not used, not only because of the limited data on their effectiveness, but also for their toxicity and carcinogenic effects.
Topical minoxidil (2% or 5%) is a vasodilator drug, which is used topically to treat different forms of hair loss (e.g., male androgenetic alopecia, female androgenetic alopecia, alopecia areata and other). Even if exact mechanism of action is not well understood, it appeared possible that, by widening blood vessels, minoxidil allows more oxygen and nutrients to the hair follicles. Regarding its potential use in vitiligo treatment, only the study of Srinivas et al. reported its efficacy. The authors described how the association of the daily use of topical 2% minoxidil with alternate day PUVA, was able to induce local hyperthricosis and marker repigmentation in 2 vitiligo patients. Unfortunately, no other studies about minoxidil in vitiligo have been conducted and some clinical reports described controversial results, such as the appearance of leucoderma after the use of the drug.

Topical cream containing pseudocatalase has been proposed as a therapeutic tool for vitiligo. The drug acts by reducing the free radicals and improving the catalase action. Generally, it is applied twice-daily. Better results appeared to be achieved when pseudocatalase is associated to sol-therapy, UVA or nb-UVB. However, not all the research confirmed these data: some studies described how the use of pseudocatalase, alone or in association with UVR, did not add any benefits.

Gianfaldoni and colleagues (2018b) noted that Neovir is an intramuscular immunomodulatory agent, composed of sodium oxo – dihydro – acridinyl - acetate (ODHAA). It is usually used to normalize impaired immune system functions under various conditions, such as viral infections, immunodeficiency, oncological diseases and multiple sclerosis. An experimental study evaluated the efficiency of acridone acetic acid, sodium salt, in stopping active non-segmental vitiligo progression. A total of 60 patients with active non-segmental vitiligo were treated with ten intramuscular injections, every 48 hours, of
ODHAA. Vitiligo progression was assessed in 1, 3, 6 and 12 months after treatment. The results of the preliminary study were excellent: sodium oxodihydroacridinylacetate showed high efficiency in achieving long-term stabilization of non-segmental vitiligo. These preliminary findings need to be validated by well-designed studies.

**Carbon Dioxide Fractional Laser**

Chen and colleagues (2018) noted that tacrolimus is a conventional medication for the treatment of vitiligo, but the effect of a single medication is limited. These researchers examined the effects, adverse responses, and re-pigmentation results of the joint treatment of vitiligo by carbon dioxide (CO2) fractional laser together with tacrolimus. A total of 45 patients with vitiligo were randomly divided into 2 groups: Treatment (T) group and control (C) group, and each group was further divided into 3 subgroups (face, torso and limbs, and hand and foot) according to the location of the skin defect. Both groups used topical 0.1% tacrolimus cream, but the T group was given 1 CO2 fractional laser treatment each month. These investigators evaluated the clinical efficacy, adverse responses, and re-pigmentation results after 6 months. Compared to the C group, the T group showed better improvement in both objective and subjective assessments. When the treatment time was increased, the efficacy was also improved, and the re-pigmentation in the T group occurred in 3 ways: peri-follicular re-pigmentation, marginal re-pigmentation as well as diffuse re-pigmentation. There were 3 cases of isomorphic responses (2 cases in the rapid progression stage, 1 case in the progression stage), and 1 case formed scarring on the neck in the T group. The authors concluded that the treatment of vitiligo by CO2 fractional laser together with tacrolimus was effective and was most suitable for patients in the progression stage. Patients in the rapid progression stage should use this approach with caution, and its efficacy was limited for patients in the stable stage. An extended course of treatment was helpful for the re-pigmentation of white patches.
All 3 forms of re-pigmentation could occur in the joint treatment of vitiligo by CO2 fractional laser together with tacrolimus. These preliminary findings need to be validated by well-designed studies.

Chiu and associates (2018) stated that the treatment of stable non-segmental vitiligo is often challenging, which new therapies are being searched. Multiple clinical trials have proposed the benefits and safety of using fractional CO2 laser as an adjunct therapy to conventional treatments. These researchers examined the safety and efficacy of fractional CO2 laser as a combination therapy to conventional treatments in patients with stable non-segmental vitiligo. They carried out a literature search using PubMed, Embase, and the Cochrane Library for comparative studies among vitiligo patients treated with additional fractional CO2 laser. Clinical outcomes in the selected studies were compared, and a meta-analysis was performed via Review Manager version 5.3, according to the PRISMA guidelines. A total of 6 studies with 184 patches/patients were included in this meta-analysis. The combination therapy group had significantly superior results than that of the control group (greater than or equal to 75% re-pigmentation, RR 2.80, 95% CI: 1.29 to 6.07; greater than or equal to 50% re-pigmentation, RR 2.26, 95% CI: 1.23 to 5.9; less than 25% re-pigmentation, RR 0.57, 95% CI: 0.43 to 0.75). The authors concluded that the findings of this meta-analysis showed that using fractional CO2 laser in combination with conventional treatments was safe and efficient, and may be considered as an adjunct therapeutic option for patients with refractive non-segmental vitiligo. Moreover, these researchers stated that the drawbacks of this study included the small number of studies (n = 6) and sample size (total of 184 patches/patients), inadequate blinding of subjects, as well as variation between therapy protocols.

Furthermore, an UpToDate review on "Vitiligo: Management and prognosis" (Grimes, 2019) does not mention carbon dioxide fractional laser as a therapeutic option.
Interleukins

Gomes and colleagues (2018) note that there is few summarized information regarding the role of inflammatory mediators, such as interleukins (ILs), in vitiligo. These investigators performed a systematic review of the role of interleukins in vitiligo. They included all studies assessing IL levels in vitiligo patients conducted up to June 2017. Quality assessment of these studies was performed using the Newcastle-Ottawa Scale (NOS). The ILs mainly involved were IL-2, IL-4, IL-6, IL-10 and IL-17. The studies highlight the crucial role of IL-17 in the onset and progression of the disease, and its synergistic action with IL-2, IL-6 and IL-33. Dysregulated levels of the ILs were also correlated with the stage of disease, the affected skin surface area, and indicated as the main factor for lymphocyte infiltration found in depigmented regions. The authors concluded that these findings showed the growing need for new therapies targeting vitiligo and further research on the role of ILs as a treatment is needed.

Furthermore, an UpToDate review on "Vitiligo: Management and prognosis" (Grimes, 2019) does not mention interleukins as a therapeutic option.

**CPT Codes / HCPCS Codes / ICD-10 Codes**

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>96910</td>
<td>Photochemotherapy; tar and ultraviolet B (Goeckerman treatment) or petrolatum and ultraviolet B</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
</tr>
<tr>
<td>96912</td>
<td>psoralens and ultraviolet A (PUVA)</td>
</tr>
<tr>
<td>96913</td>
<td>Photochemotherapy (Goeckerman and/or PUVA) for severe photoreactive dermatoses requiring at least four to eight hours of care under direct supervision of the physician (includes application of medication and dressings)</td>
</tr>
<tr>
<td>96920 - 96922</td>
<td>Laser treatment for inflammatory skin disease (psoriasis)</td>
</tr>
<tr>
<td>96999</td>
<td>Unlisted special dermatological service or procedure [excimer laser]</td>
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CPT codes not covered for indications listed in the CPB:

**Cytotoxic T-lymphocyte antigen (CTLA)-4+49A/G and TNF-alpha 308G/A polymorphism testing - no specific code:**

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<tr>
<th>Code</th>
<th>Code Description</th>
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<tr>
<td>11920 - 11922</td>
<td>Tattooing, intradermal introduction of insoluble opaque pigments to correct color defects of skin, including micropigmentation</td>
</tr>
<tr>
<td>15100</td>
<td>Split-thickness autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)</td>
</tr>
<tr>
<td>15101</td>
<td>each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)</td>
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</table>

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>J0702</td>
<td>Injection, betamethasone acetate 3mg and betamethasone sodium phosphate, 3 mg</td>
</tr>
<tr>
<td>J1020</td>
<td>Injection, methylprednisolone acetate, 20 mg</td>
</tr>
<tr>
<td>J1030</td>
<td>Injection, methylprednisolone acetate, 40 mg</td>
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<tr>
<td>J1040</td>
<td>Injection, methylprednisolone acetate, 80 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------</td>
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<tr>
<td>J1094</td>
<td>Injection, dexamethasone acetate, 1 mg</td>
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<tr>
<td>J1100</td>
<td>Injection, dexamethasone sodium phosphate, 1mg</td>
</tr>
<tr>
<td>J1700</td>
<td>Injection, hydrocortisone acetate, up to 25 mg (i.e., Hydrocortone acetate)</td>
</tr>
<tr>
<td>J1710</td>
<td>Injection, hydrocortisone sodium phosphate, up to 50 mg (i.e., Hydrocortone phosphate)</td>
</tr>
<tr>
<td>J1720</td>
<td>Injection, hydrocortisone sodium succinate, up to 100 mg (i.e., Solu-Cortef)</td>
</tr>
<tr>
<td>J2650</td>
<td>Injection, prednisolone acetate, up to 1 ml (i.e., Key-Pred 25, Key-Pred 50, Predcor-25, Predcor-50, Predcor-50, Predoject50, Predalone-50, Predicort-50)</td>
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<td>Injection, methylprednisolone sodium succinate, up to 40 mg (i.e., Solu-Medrol)</td>
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<td>Injection, methylprednisolone sodium succinate, up to 125 mg (i.e., Solu-Medrol)</td>
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<td>J3301</td>
<td>Injection, triamcinolone acetonide, per 10 mg (i.e., Kenalog)</td>
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<td>J3302</td>
<td>Injection, triamcinolone diacetate, per 5 mg (i.e., Aristocort)</td>
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<td>Injection, triamcinolone hexacetonide, per 5 mg (i.e., Aristospan)</td>
</tr>
<tr>
<td>J7509</td>
<td>Methylprednisolone, oral, per 4 mg</td>
</tr>
<tr>
<td>J7510</td>
<td>Prednisolone, oral, per 5 mg</td>
</tr>
<tr>
<td>J7512</td>
<td>Prednisone, immediate release or delayed release, oral, 1 mg</td>
</tr>
<tr>
<td>J8540</td>
<td>Dexamethasone, oral, 0.25 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>A4633</td>
<td>Replacement bulb/lamp for ultraviolet light therapy system, each</td>
</tr>
<tr>
<td>E0691</td>
<td>Ultraviolet light therapy system panel, includes bulbs/lamps, timer, and eye protection; treatment area two square feet or less</td>
</tr>
<tr>
<td>E0692</td>
<td>Ultraviolet light therapy system panel, includes bulbs/lamps, timer, and eye protection, four foot panel</td>
</tr>
<tr>
<td>E0693</td>
<td>Ultraviolet light therapy system panel, includes bulbs/lamps, timer, and eye protection, six foot panel</td>
</tr>
<tr>
<td>E0694</td>
<td>Ultraviolet multidirectional light therapy system in 6 foot cabinet, includes bulbs/lamps, timer, and eye protection</td>
</tr>
<tr>
<td>J0135</td>
<td>Injection, adalimumab, 20 mg</td>
</tr>
<tr>
<td>J0636</td>
<td>Injection, calcitriol, 0.1 mcg</td>
</tr>
<tr>
<td>J1438</td>
<td>Injection, etanercept, 25 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)</td>
</tr>
<tr>
<td>J1745</td>
<td>Injection, infliximab, 10 mg</td>
</tr>
<tr>
<td>J2501</td>
<td>Injection, paricalcitol, 1 mcg</td>
</tr>
<tr>
<td>J9312</td>
<td>Injection, rituximab, 10 mg</td>
</tr>
<tr>
<td>Q5103</td>
<td>Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg</td>
</tr>
<tr>
<td>Q5104</td>
<td>Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Q5109</td>
<td>Injection, infliximab-qbtx, biosimilar, (Ixifi), 10 mg</td>
</tr>
<tr>
<td>S0161</td>
<td>Calcitrol, 0.25 mcg</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- **L80** Vitiligo

Human leukocyte antigen-A polymorphism testing - no specific code:

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- **L80** Vitiligo

Protein tyrosine phosphatase:

CPT codes not covered for indications listed in the CPB:

- **86341** Islet cell antibody

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- **L80** Vitiligo

NLPR1 gene polymorphisms testing - no specific code:

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- **L80** Vitiligo

Polyarteritis nodosa and related conditions:

**CelluTome Epidermal Harvesting System**:

CPT codes not covered for indications listed in the CPB:

- **15110** Epidermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children

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<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15111</td>
<td>Epidermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>15115</td>
<td>Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children</td>
</tr>
<tr>
<td>15116</td>
<td>Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L80</td>
<td>Vitiligo</td>
</tr>
</tbody>
</table>

Janus kinase inhibitors:

HCPCS codes not covered for indications listed in the CPB:

Janus kinase inhibitors (e.g., ruxolitinib and tofacitinib) - No specific code:

Prostaglandins and prostaglandin E2:

CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>84150</td>
<td>Prostaglandin, each</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L80</td>
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</tr>
</tbody>
</table>

Aprimalist, Topical phenytoin gel, Glutathion, Melagenin, Topical minoxidil, Topical pseudocatalase, Nevoir, Carbon dioxide fractional laser - no specific code:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
<td></td>
</tr>
<tr>
<td>L80</td>
<td>Vitiligo</td>
</tr>
<tr>
<td>Capecitabine:</td>
<td></td>
</tr>
<tr>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>J2355</td>
<td>Injection, oprelvekin, 5 mg</td>
</tr>
<tr>
<td>J8520</td>
<td>Capecitabine, oral, 150 mg</td>
</tr>
<tr>
<td>J8521</td>
<td>Capecitabine, oral, 500 mg</td>
</tr>
<tr>
<td>J9015</td>
<td>Injection, aldesleukin, per single use vial</td>
</tr>
<tr>
<td>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</td>
<td></td>
</tr>
<tr>
<td>L80</td>
<td>Vitiligo</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


55. Goldstein BG, Goldstein AO. Vitiligo. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2013.


61. Goldstein BG, Goldstein AO. Vitiligo. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed March 2014.


Gene Polymorphisms Testing for Early Detection of Vitiligo


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0422 Vitiligo

There are no amendments for Medicaid.