Updates and new medical treatments for vitiligo (Review)

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Abstract. Vitiligo is a multifactorial disease characterized by the loss of skin pigment, which results in achromic macules and patches. There are currently several medical treatments available, which aim to arrest progression and induce skin repigmentation. These treatments alone or combined have exhibited varying degrees of pigmentation, and the majority are safe and effective. All therapies for vitiligo are limited, and no known treatment can consistently produce repigmentation in all patients. Individualized treatment is appropriate according to the location, clinical presentation and the presence of disease activity. The present review summarizes the medical treatments available for vitiligo: Systemic and topic pharmacological therapies, physical and depigmentation treatments. Several treatments are still underway and have not yet been approved. However, due to the promising preliminary results, these are also mentioned in the present review.

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1. Introduction

Vitiligo is the most common disorder of depigmentation, and in 2012 its worldwide prevalence ranged from 0.06-2.28% (1,2). It is characterized by the absence of pigment in the skin, secondary to the loss of melanocytes (1,3). Melanocytes are found in several tissues in the skin, hair follicles, eyes, inner ear, bones, heart and brain (4). Melanocytes are found in the basal layer of the epidermis and together with the surrounding keratinocytes form the epidermal unit, whose main function is to produce and distribute melanin by a complex process called melanogenesis (4-7). Melanin is a pigment with two forms, eumelanin (brown/black or black) and pheomelanin (red/yellow) (6,8). It has light-absorbing properties that confer photoprotection (4,6-8). Melanogenesis is determined genetically but is influenced by several intrinsic and extrinsic factors (5). The intrinsic factors are released by surrounding cells, including keratinocytes, fibroblasts, inflammatory, neural and endocrine cells (4,5,9,10). The extrinsic factors include ultraviolet radiation and drugs (5). Among the inducers and positive regulators of melanogenesis are L-tyrosine and L-DOPA (pigment precursors), ultraviolet radiation and the melanocortin 1 receptor (5,9,10). The latter is considered the most important positive regulator (5,9,10).

The pathogenesis of vitiligo is unknown, but an autoimmune hypothesis prevails and is supported by several factors: Its association with other autoimmune diseases, the high level of antibodies against melanocytes found in 10% of patients with vitiligo, susceptibility loci associated with vitiligo found

in genome-wide association studies that encode immunomodulatory proteins, and lastly, an inflammatory infiltrate that is observed at the margin of active lesions (11,12). In the biochemical theory, the damage to melanocytes is due to an imbalance in oxidative stress; a higher level of hydrogen peroxide in patients with vitiligo and increased superoxide dismutase activity reinforce this theory (11). Another hypothesis is the melanocytorrhagy theory, which proposes that defective cell adhesion leads to detachment and transepidermal loss of melanocytes with exposure of autoantigens and activation of the immune system leading to melanocyte injury (3). Finally, the convergence theory states that a combination of several pathways is necessary for the development of vitiligo, such as genetic background, susceptibility to environmental changes, altered epidermal microenvironment, an intrinsic melanocyte defect and an autoimmune response (13,14). Clinically, vitiligo manifests as achromic macules and patches that increase in number and size over time (15). Treatment strategies aim to arrest the disease, achieve repigmentation and prevent relapse (16). The present review discusses the pharmacological, physical and depigmentation treatment options for vitiligo, used either as monotherapy or in combination. In general, combining therapies results in superior outcomes (17).

2. Pharmacological treatment

Topical treatment

Corticosteroids. Corticosteroids' main therapeutic effect in vitiligo is modulation and inhibition of inflammation (18). Topical corticosteroids (TCS), either potent (betamethasone valerate) or very potent (clobetasol propionate), are considered first-line therapy for vitiligo (19,20). The sun-exposed areas have a better response to treatment, while acral regions generally exhibit a poor response (18). High potency TCS are recommended to treat small areas of the body; in the areas more sensitive to TCS, namely the face, neck, genitals or intertriginous regions where absorption may be higher and more side effects may present, topical calcineurin inhibitors (TCI) or lower potency steroids are preferred (21,22). The application of daily TCS for up to 3 months is recommended (18). After that, an intermittent regimen can be used for up to 6 months, and if no response is seen after 3-4 months, the application should be discontinued (18,21,23). In a meta-analysis, Njoo *et al* (20) reported the effectiveness of TCS in localized vitiligo, measured as the percentage achieving ≥75% repigmentation, which was comparable with potent (56%) and very potent (55%) TCS. To increase the probability of a therapeutic response when TCS is used as monotherapy, very potent TCS may be preferred (17).

The side effects of TCS include atrophy, striae, telangiectasias, hypertrichosis and acneiform reactions (18). The most frequent local side effect is atrophy, which depends on diverse factors, including age, site of application, the potency of the TCS and the presence of occlusion. In vitiligo, sometimes long treatments are required (24). 'Corticosteroid holidays' which are weeks without TCS, along with tapering from high to mild potency can be used to minimize side effects (24). In addition to local side effects, systemic absorption may cause adrenal suppression (25). Kwinter *et al* (25) performed a retrospective study in pediatric patients with vitiligo treated with moderate to high potency TCS. The results demonstrated that cortisol levels were abnormal in 29% of patients, and the potential risks associated were lesions located in the head and neck (25). These undesirable effects can be minimized in the pediatric population by using soft steroids, which are esterified corticosteroids that retain their anti-inflammatory effects and have fewer systemic side effects (26), including mometasone furoate and methylprednisolone aceponate (26).

Calcineurin inhibitors. Calcineurin inhibitors are immunomodulators and an off-label treatment for vitiligo (24). They function by inhibiting calcineurin, a pro-inflammatory protein in lymphocytes and dendritic cells that induces the transcription of interleukin (IL)-2 and tumor necrosis factor-α (TNF-α) (27). Its inhibition decreases cytokine formation, and induces melanocyte and melanoblast proliferation (27). TCIs, such as tacrolimus (0.03 or 0.1%) and pimecrolimus (1%) are recommended for the head and neck areas as they have less side effects, mainly the lack of atrophy risk (18,21). TCI can be applied twice daily for a minimum of 6 months. When beneficial effects are observed, treatment can be prolonged according to results (18). Moderate daily sun exposure is recommended during treatment (18). Another usage of TCI is during the intermittent treatment schemes of TCS, whereby on days TCS was not applied, TCI can be used to ensure a continuous treatment (22).

The efficacy of TCI as monotherapy in a systemic review and meta-analysis by Lee *et al* (28), demonstrated ≥25% repigmentation in 55%, ≥50% repigmentation in 38.5%, and ≥75% repigmentation in 18.1% of patients. The results in children were ≥25% repigmentation in 66.4% and ≥75% repigmentation in 31.7% patients. A better response was achieved on the face and neck followed by the trunk and extremities and the least response was observed in the hands and feet (28). In a meta-analysis by Chang *et al* (29), comparing the efficacy of TCI to TCS, TCI was less effective than TCS in achieving ≥50% repigmentation but was comparable to TCS in achieving ≥75% repigmentation (29).

TCI can be used as monotherapy or in combination. Ebrahim *et al* (30) performed a study comparing the application of tacrolimus 0.1% alone or in combination with microneedling (fine needles to create micro-holes in the skin) in patients with localized stable vitiligo. Both groups applied tacrolimus daily, but the combination group also received microneedling and tacrolimus application every 2 weeks for up to 12 sessions. The results exhibited earlier pigmentation and ≥75% pigmentation in 50.00% of patients in the combination group compared with 29.92% in the monotherapy group (30).

Another combination was studied by Abd-Elazim *et al* (31) in a randomized placebo-controlled study in patients with stable generalized vitiligo. In each patient, three lesions of similar size were chosen. One lesion was treated with tacrolimus 0.03% daily, another with a combination of monthly microdermabrasion (light abrasion of the skin) and daily tacrolimus 0.03%, and the last was treated with placebo. The combination group achieved moderate to excellent response (≥50% repigmentation) in 65.7% of lesions compared with monotherapy with tacrolimus in 25.8% of lesions (31).

The side effects of TCI include burning sensation, pruritus and increased susceptibility to infection (herpes simplex and molluscum contagiosum) (24).

Vitamin D3 analogs. Vitamin D sources are the diet or synthesis by the skin with UVB light from 7-dehydrocholesterol (32,33). The classical pathway to obtain the hormonally active form of vitamin D is by hydroxylation to 25-hydroxyvitamin D3; mainly in the liver, and it is subsequently converted to 1,25-hydroxyvitamin D3 in the kidney, which is the active form of the vitamin (32,33). An alternative pathway of vitamin D3 activation is the biologically active metabolites produced by the action of cytochrome P450 family 11 subfamily A member 1 (CYP11A1) (34-37). Another source of active vitamin D3 is through the synthesis by antigen-presenting cells, T cells and B cells (38). These cell types can also respond to the stimulation of vitamin D, which may be associated with the ability to maintain self-tolerance and to promote protective immunity against infections (38).

Topical vitamin D3 analogs (D3A) are not effective as monotherapy for vitiligo but are useful as adjuvants to other therapies due to their immunomodulatory effects inhibiting T-cell activity, enhancement of melanocyte development and induction of melanogenesis (27,39,40). The maximum recommended dose is 100 g weekly on 30% of the body surface with the combination of calcipotriol 0.005% and betamethasone 0.05% for 4 weeks using the ointment and 8 weeks for the cream (24).

Efficacy of the combination therapy calcipotriol 0.005% and betamethasone dipropionate 0.05% was studied by Kumaran *et al* (41) in a randomized controlled trial, where each drug was given alone or in combination to patients with localized vitiligo. Marked repigmentation (50-75%) was achieved in 6.7% of patients in the calcipotriol, 13.3% in the betamethasone and 26.7% in the combination groups, respectively. Moderate repigmentation (25-50%) was observed in 33.3% of patients in the calcipotriol, 46.7% in the betamethasone and 46.7% in the combination groups, respectively. No patient achieved >75% repigmentation, but combined therapy resulted in faster repigmentation (41).

The transdermal delivery of drugs may be increased using microneedling. This was studied by Ibrahim *et al* (42) with the combination of microneedling with calcipotriol 0.05 mg/g and betamethasone 0.5 mg, compared with microneedling with tacrolimus 0.03%. The patients received both therapies in two different lesions. The creams were applied daily and microneedling was performed every 2 weeks for a maximum of 12 sessions. The combination with calcipotriol and betamethasone exhibited 76-100% repigmentation in 60% of patients compared with 32% in the combination with tacrolimus, concluding that the combination of calcipotriol and betamethasone with microneedling was superior and also effective in sites resistant to therapy (elbow, knees, extremities and acral area) (42). D3A is safe in both children and adults, only mild irritation has been reported (24).

Pseudocatalase/superoxide dismutase. Oxidative stress and accumulation of hydrogen peroxide (H_2O_2) are believed to play roles in vitiligo. High levels of H_2O_2 accumulate in the epidermis of the lesions (43). These are toxic to melanocytes, inhibit tyrosinase, and cause the deactivation of catalase (a peroxisomal enzyme catalyzing the reduction of H_2O_2 to water and oxygen) (43). The efficacy of topical pseudocatalase is variable. In a pilot, randomized, placebo-controlled trial performed by Naini *et al* (43) using topical pseudocatalase/superoxide dismutase gel, no significant changes in the lesion area and perifollicular pigmentation were observed. In a study performed in a pediatric population by Schallreuter *et al* (44), patients were treated with twice daily application of pseudocatalase PC-KUS activated with low-dose narrow-band UVB (nb-UVB). The results demonstrated a halt of disease progression in 70/71 patients; >75% repigmentation was achieved in 92.9% of children with lesions located on the face/neck, 78.6% on the trunk, 72.7% on the extremities and 9.4% on the hands/feet (44). Bakis-Petsoglou *et al* (45) evaluated topical pseudocatalase and nb-UV in a double-blind, placebo-controlled, randomized, single-center trial in patients with active vitiligo. No added benefit was observed with the combination therapy (45). A study performed by Alshiyab *et al* (46), comparing the efficacy of tacrolimus 0.1% ointment to tacrolimus 0.1% ointment plus topical pseudocatalase/superoxide dismutase gel in the treatment of children with localized vitiligo, demonstrated that there was no significant difference in repigmentation percentages between the two groups. However, information on side effects and safety of pseudocatalase is lacking (47). Current data are not in favor of an additional effect of topical catalase compared with UVB alone (45).

5-gluorouracil (5-FU). Topical 5-FU is mainly used for the treatment of premalignant and malignant skin lesions (48). The observation of hyperpigmentation following therapy with this drug led to its use in vitiligo (48). The mechanisms of repigmentation of 5-FU may include stimulation of follicular melanocytes with migration during epithelization and by increasing the number of melanosomes in keratinocytes (49,50). The efficacy of monotherapy with 5-FU has been reported by Tsuji-Takuo and Hamada (48). A 5-FU cream was applied following epidermal abrasion, once daily for 7-10 days and >75% repigmentation was observed in 64% of patients (48).

Several studies have combined laser therapy with topical 5-FU (49,51,52). Abdelwahab *et al* (49) performed a study to assess the effect of 5-FU in monotherapy compared with its combination with ablative erbium: YAG (2,940 nm) laser in non-segmental vitiligo. Erbium: YAG laser was applied using the surgical handpiece with a spot size of 4 mm and a fluence of 60 J/cm^2. A total of two to three passes were given with an endpoint of pinpoint bleeding, receiving three treatment sessions every 4-6 weeks. 5-FU cream was used daily for 2 weeks after each session. The range of repigmentation in the combined treatment was 0-70%, with <25% repigmentation in 73.3 and 50-75% repigmentation in 10% of patients; the range of repigmentation in the monotherapy group was 0-5% (49). Anbar *et al* (51) also used erbium-YAG laser in combination with topical 5-FU but in periungual vitiligo. The laser was used with a spot size of 5 mm and a fluence of 2.1 J/cm^2. The endpoint was pinpoint bleeding with usually three passes required. Topical 5-FU cream was applied daily until inflammation with erythema, moderate oozing and crustation occurred. The sessions with erbium-YAG laser were repeated until 100% repigmentation was achieved or for a maximum of three successive sessions performed with no further improvement observed. The results were ≥75% repigmentation in

33.3% of patients, 26-74% repigmentation in 33.3 and ≤25% repigmentation or none in 33.3% (51).

CO_2 laser with topical 5-FU was studied in acral vitiligo by Mohamed *et al* (52). The laser was employed at a rate of 1-2 Hz in level 2 pulse control and a power of 0.9 W to deliver single pulses using the single-spot handpiece. In the abraded area, 5-FU was applied daily for 7 days, and CO_2 laser sessions were repeated monthly until healing or a maximum of 5 sessions. The results demonstrated >75% repigmentation in 49.8% of the lesions and 50-75% repigmentation in 6.1% of the lesions (52).

Mina *et al* (53) performed a study comparing microneedling with either topical tacrolimus or topical 5-FU. In each patient, two patches of vitiligo were treated. First, microneedling with a Dermapen at the lowest speed and a depth of 0.25-0.50 mm according to the area was performed, then one patch was treated with a solution of 5-FU (50 mg/ml) and the other with tacrolimus 0.03% ointment. Patients were advised to continue the treatment with daily application of either 5-FU or tacrolimus for 2 weeks, accordingly. Microneedling in combination with topical treatment was repeated every 2 weeks for a maximum of 12 sessions. The reported efficacy with the combination of 5-FU was >75% repigmentation in 48% of patients, 51-75% repigmentation in 4 and 26-50% repigmentation in 20% of patients compared with 16, 24 and 36%, respectively, in the tacrolimus group. The 5-FU group also presented a faster response to repigmentation (53). The side effects of 5-FU are hyperpigmentation, scarring, infection, ulceration and delayed wound healing (47,53).

Methotrexate (MTX). MTX is a folate antagonist that appears to decrease the number of T cells producing TNF-α, consequently having anti-inflammatory, immunomodulatory and antiproliferative effects (54). In a recent case report (54) in a patient with stable vitiligo, significant repigmentation was observed following treatment with topical MTX 1% gel applied twice daily for 12 weeks, along with folic acid supplementation. No side effects were reported. However, further studies are required to determine the efficacy and safety of MTX (54).

Prostaglandin F2 alpha analogs. Treatment of ocular hypertension with prostaglandin F2 alpha analogs (PF2A) is common (55). The observation of iris and periocular skin hyperpigmentation in patients with glaucoma led to its use in vitiligo (55). This hyperpigmentation seems to be due to an increase in melanogenesis (56).

In a preliminary study performed by Kanokrungsee *et al* (57), the efficacy of bimatoprost 0.01% solution was assessed in patients with non-segmental facial vitiligo compared with tacrolimus 0.1% ointment. Both topical drugs were applied twice daily for 12 weeks. Repigmentation was observed in 60 and 50% of the patients in the bimatoprost and tacrolimus groups, respectively. In addition, >50% repigmentation was achieved in 20% of patients in the bimatoprost group compared with 10% in the tacrolimus group, although no statistically significant differences were observed between the two groups (57). Latanoprost efficacy was evaluated in a double-blind clinical control trial by Nowroozpoor Dailami *et al* (58). Patients enrolled had generalized or focal vitiligo involving the eyelids. Latanoprost 0.005% gel was applied twice daily for 12 weeks and was compared with placebo. Improvement in pigmentation was observed in 45.66±14.87 and 2.32±0.85% in the case and control groups, respectively (58). The side effects of PF2A are minimal and periorbital hyperpigmentation is infrequent (24).

Basic fibroblast growth factor (bFGF)-derived peptide. bFGF effect in vitiligo is through melanocyte migration (59). The efficacy of bFGF as monotherapy was assessed by Kamala Subhashini *et al* (59) in a comparative study in patients receiving monotherapy with either bFGF 0.1% solution or betamethasone valerate 0.1% ointment. Both groups applied their respective drug daily for 16 weeks. The bFGF group reported >75% repigmentation in 45% of patients, 50-75% repigmentation in 35 and <50% repigmentation in 20%, compared with 0, 7 and 13%, respectively, in the betamethasone group. Also, 80% of patients exhibited no response in the betamethasone group (59). Shah *et al* (60) performed an open-label, randomized, prospective study using bFGF related decapeptide solution in combination with tacrolimus 0.1% ointment compared with monotherapy with tacrolimus 0.1% in patients with stable vitiligo. Both treatments were applied daily. The interim analysis at 6 months was >50% repigmentation in 22.5% of patients in the combination group compared with 6.8% of patients in the monotherapy group (60). The side effects include dry skin, burning sensation and skin irritation (24).

Janus kinase (JAK) inhibitors. JAK inhibitors used in vitiligo are tofacitinib (a JAK1/3 inhibitor) and ruxolitinib (a JAK 1/2 inhibitor) (61). Their mechanism of action is through downregulation of the JAK-STAT pathway, which decreases interferon-gamma (IFN-γ), which is also associated with the cell-mediated immunity in vitiligo (61). Hamzavi *et al* (62) performed a phase 2 open-label trial study with 11 patients with vitiligo. Ruxolitinib 1.5% cream was applied twice daily for 20 weeks in up to 10% of the body surface area or 3.75 g per application. Results were evaluated using the vitiligo area scoring index (VASI) (62), with a statistically significant overall mean improvement of 27% in patients who completed the trial, with a better response in lesions located in the face than in other sites (63). A recent phase 2 study by Rosmarin *et al* (64) evaluated the efficacy and safety of ruxolitinib cream at three different concentrations (0.15, 0.5 and 1.5%) compared with placebo, for up to 52 weeks. Patients were classified into four different groups of ruxolitinib: 1.5% twice daily, 1.5% once daily, 0.5% once daily and 0.15% once daily. Efficacy was evaluated using the percentage of patients achieving ≥50% improvement in the baseline facial VASI (F-VASI50). The ruxolitinib 1.5% once and twice daily groups achieved a F-VASI50 in 50 and 45% of patients, respectively, at 24 weeks compared with 3% in the placebo group (64).

Mobasher *et al* (65) performed an open-label study with tofacitinib 2% cream twice daily in 16 patients with vitiligo. Notably, patients were allowed concomitant use of TCS, TCI, supplements, or phototherapy during the study. Repigmentation was observed in 81.2% of patients. In addition, >90% repigmentation was observed in four patients, 25-75% repigmentation in five patients, 5-15% repigmentation in four patients, no change in two patients, and slow progression in one patient, with more improvement in facial lesions compared with other sites (65).

The side effects of JAK inhibitors include erythema, pruritus, hyperpigmentation and transient acne (63,64).

Systemic treatment

Corticosteroids. The main objective of systemic corticosteroids (SCS) use is to suppress the immune response, and with that stabilize the disease, favoring repigmentation (66). SCS is administrated to treat rapidly progressive active vitiligo (18). Pulse therapy with SCS is preferred to decrease the potential side-effects (67). Patients undergoing therapy with SCS should be monitored for blood pressure, glucose levels, weight, waist circumference and infections, as well as an ophthalmic examination every 6-12 months (24).

Several schemes for SCS have been reported. Imamura and Tagami (68) performed a study on 17 patients with generalized vitiligo and five patients with localized vitiligo. They used several oral corticosteroids (prednisolone, betamethasone, paramethasone acetate and methylprednisolone) at different doses, which were gradually decreased to a maintenance dose; effectiveness was assessed at 6 months. The results demonstrated >75% pigmentation in at least one patch in 35% of patients with generalized vitiligo, and repigmentation became evident at 4 weeks in most cases (68). Kim *et al* (66) also performed a study with continuous use of SCS in patients with active vitiligo. Oral prednisolone was given the first 2 months at 0.3 mg/kg of body weight, the third month at half of the initial dose, and the fourth month at half of the previous dose. The results exhibited arrest of vitiligo progression in 87.7% of patients and repigmentation in 70.4% of patients (66). Using the same scheme, Banerjee *et al* (69) observed arrest in 90% of patients and repigmentation in 76% of patients with active vitiligo.

Pasricha and Khaitan (70) used a therapy based on pulses of either betamethasone or dexamethasone at 5 mg orally for 2 consecutive days every week; treatments were continued until complete repigmentation or 4 months of continuous treatment with no further improvement. The results were halt in active disease in 89% of patients with 5 mg dose after 1-3 months and repigmentation was observed in 80% of patients after 2-4 months of treatment. The extent of repigmentation was 76-99% in 15.0% of patients, 51-75% in 7.5% of patients, 26-50% in 25.0% of patients, 10-25% in 17.5% of patients and <10% in 35.0% of patients (70). Kanwar *et al* (71) reported a retrospective study with a cohort of 444 patients with active vitiligo, using a low-dose oral mini-pulse therapy with a dose of 2.5 mg/day on 2 consecutive days every week. Arrest in disease activity was achieved in 91.8% of patients, during follow up 12.25% of these patients experienced one or two relapses in activity (71). Another scheme of oral pulse therapy was used by Radakovic-Fijan *et al* (72) administering 10 mg of dexamethasone 2 consecutive days for 24 weeks. The arrest of vitiligo activity was achieved in 88% of patients with active vitiligo and most of the patients (72.4%) had no response to repigmentation (72).

Seiter *et al* (67) also implemented a therapy based on pulses but with an intravenous route. Methylprednisolone was intravenously administered for 3 consecutive days at a dose of 8 mg/kg of body weight. The treatment was repeated at 4 and 8 weeks if tolerated. Active vitiligo progression was halted in 85% of patients and repigmentation in 71% of patients. Patients with stable vitiligo had no change in pigmentation (67).

The side effects of SCS are weight gain, transient weakness, fatigue, insomnia, acne, agitation, menstrual disturbances, hypertension, metallic taste, pruritus, headache, flush symptoms and hypertrichosis (67,70,72).

Apremilast. Apremilast is a phosphodiesterase 4 inhibitor that acts by increasing intracellular cyclic adenosine monophosphate (cAMP) (73). Apremilast application in vitiligo is due to its immunomodulation properties, increasing cAMP concentration results in the decreased production of pro-inflammatory mediators (IL-23, IL-17, TNF-α and IFN-γ) and an increase in anti-inflammatory mediators, such as IL-10 (73). Apremilast is approved for the treatment of moderate to severe plaque psoriasis (73). The first case report of its use in vitiligo was by Huff and Gottwald (74) in a patient that failed other therapies. Apremilast (30 mg twice daily) was administered for 13 months, and two intramuscular injections of 60 mg of triamcinolone acetonide were simultaneously applied. The results were repigmentation in 60-70% of the chest and extremities (74). More recently, a pilot study performed by Majid *et al* (73) reported a case series of 13 patients with rapidly progressing non-segmental vitiligo treated with apremilast 30 mg twice daily for 3 months after initial titration. The patients could use topical tacrolimus on the exposed parts of the body. The results were stabilization in all patients and partial repigmentation in 61.5% of patients (73). The side effects of apremilast include headache, nausea, vomiting, weight loss, depression and abdominal pain (73,74).

JAK inhibitors. JAK inhibitors are not only topically used. Craiglow and King (75) reported the case of a 50-year-old female with widespread and progressive vitiligo treated with oral tofacitinib citrate 5 mg daily for 5 months, with nearly complete repigmentation of the forehead and hands, while other areas exhibited partial repigmentation (75). Improvement of vitiligo was also observed in two case reports of female patients treated with tofacitinib 5 mg twice daily for rheumatoid arthritis (76,77). Liu *et al* (61) reported a case series of 10 patients treated with tofacitinib 5-10 mg, once or twice daily for at least 3 months. During the study, suction blister sampling was performed on responding and nonresponding areas, revealing an inhibition of the autoimmune response in both. Repigmentation was observed in 50% of patients at sites of low-dose nb-UVB phototherapy or sun-exposed areas; with these findings, the authors suggest that low-level light may be required for melanocyte regeneration and repigmentation during treatment with JAK inhibitors (61). The side effects were upper respiratory infections, weight gain, arthralgia and mild elevation of lipid levels (61).

Minocycline. This oral antibiotic was studied as a therapeutic option for vitiligo after *in vitro* analysis suggested that minocycline protects melanocytes from oxidative stress and prevents their loss in the early stages of the disease (78). To evaluate this, Parsad and Kanwar (79) performed a study on 32 patients with gradually progressive vitiligo. Patients were treated with 100 mg of minocycline daily for 3 months, the arrest of activity was achieved in 90.6% of patients, and moderate to marked repigmentation was observed in 21.8% of patients (79). Singh *et al* (80) performed a randomized

controlled study to evaluate the efficacy and tolerability of oral minocycline compared with oral mini-pulse corticosteroids in patients with active vitiligo. The minocycline group received 100 mg daily, while the corticosteroid group received dexamethasone 2.5 mg on 2 consecutive days every week. Efficacy was evaluated using the vitiligo disease activity score (VIDA) (81) and VASI. Although not statistically significant at the end of treatment, VIDA and VASI scores decreased in both groups with comparable results, suggesting both drugs are effective to halt vitiligo activity (80). Another prospective comparative trial by Siadat *et al* (82) compared minocycline 100 mg daily to nb-UVB phototherapy in patients with unstable vitiligo during 3 months of treatment. Vitiligo was active in 100% of patients at the beginning of the trial; however, this decreased to 66.1 and 23.8% in the minocycline and nb-UVB groups, respectively, following treatment (82). The side effects of minocycline are nausea, gastrointestinal complaint, headache, and hyperpigmentation of the nails, oral mucosa or skin (80,82).

Statins. Statins are lipid-lowering drugs. Their role in vitiligo is due to anti-inflammatory and immunomodulatory effects that cause inhibition of CD8 T-cell proliferation, chemokines, proinflammatory mediators, and the expression of proinflammatory adhesion molecules (83,84). In addition, inhibition of IFN-γ production decreases the expression of major histocompatibility complex II and inhibition of activated T cell (83-86). Statins also exert antioxidant properties by upregulating the transcription factor nuclear erythroid 2-related factor, resulting in a reduction of reactive oxygen species and activation of the antioxidant response in melanocytes (83). Statins increment the production of tyrosinase mRNA and increase the effect of α-melanocyte-stimulating hormone on melanocytes resulting in improved melanogenesis (83). There is only one case report of unexpected improvement of vitiligo in a patient treated with a high dose of simvastatin (87). However, studies using statins have reported no benefit in vitiligo (85,86,88).

MTX. MTX is commonly used for multiple inflammatory and autoimmune diseases (89). Most of the initial reports of improvement in vitiligo treated with MTX were in patients using it for concomitant rheumatoid arthritis or psoriatic arthritis. The dosage of MTX varied from 7.5-25.0 mg weekly, along with folic acid supplementation. The results ranged from arrest in vitiligo activity to significant repigmentation (89,90). In a prospective study performed by Nageswaramma *et al* (91), 20 patients with unstable vitiligo were treated with MTX 15 mg weekly and folic acid supplementation. The results were moderate repigmentation in 70% of patients and arrest in progression in 90% of patients. However, the efficacy of MTX in vitiligo is variable. In an uncontrolled pilot study by Alghamdi and Khurrum (89), no clinical improvement was observed with MTX 25 mg weekly for 6 months. A randomized comparative study performed by Singh *et al* (92) compared MTX 10 mg weekly to oral corticosteroid mini pulses with 2.5 mg of dexamethasone on 2 consecutive days for 24 weeks. Both groups had a similar reduction in the VIDA score at the end of the study. New lesions developed during treatment in 23% of patients in the MTX group and 28% of patients in the corticosteroid group (92). ElGhareeb *et al* (93) performed a study with 42 patients to assess the efficacy and safety of oral MTX and oral mini pulse of dexamethasone, used either alone or in combination. Patients were randomly divided into three groups. Group A received 15 mg of MTX divided into three doses, with a 12 h weekly interval. Group B received 5 mg of dexamethasone daily on 2 successive days every week. Group C received a combination of both protocols. All groups received the treatment for 3 months. The results demonstrated a significant decrease in disease extension in group C compared with the other groups (93). The side effects of MTX are hepatotoxicity, idiosyncratic pulmonary toxicity, pancytopenia, nausea, vomiting and diarrhea (24).

Azathioprine. Azathioprine is an immunosuppressant that inhibits DNA synthesis in immune effector cells (47). There is a study of its use in vitiligo performed by Madarkar *et al* (94), comparing azathioprine 50 mg twice daily to betamethasone 5 mg on 2 consecutive days every week for 6 months. Remarkable improvements were observed in both groups, and the authors suggest that both therapies are equally effective in vitiligo (94). Radmanesh and Saedi (95) performed a study on 60 patients randomized into two groups. The first group received azathioprine calculated at 0.60-0.75 mg/kg per day (maximum dosage 50 mg) combined with twice-weekly oral psoralen (methoxypsoralen 0.3-0.4 mg/kg) plus UVA. The second group only received oral psoralen plus UVA (PUVA). Both groups were followed for 4 months. The results exhibited earlier repigmentation at 5 oral PUVA sessions and greater repigmentation (58.4%) in the combination group compared with the oral PUVA monotherapy group at 8 sessions with 24.8% repigmentation (95). The side effects of azathioprine include myelosuppression, hepatotoxicity, gastric irritation, increased susceptibility to infections (herpes simplex and human papillomavirus) and hypersensitivity syndrome (24).

Cyclosporine. Cyclosporine is a calcineurin inhibitor with immunomodulatory action. Taneja *et al* (96) performed an open-label, single-arm study in 18 patients with progressive vitiligo using cyclosporine at a dose of 3 mg/kg/day, divided into two doses for 12 weeks. Progression of vitiligo was arrested in 61% of the patients and repigmentation was observed in 81% of the patients (96). A pilot study was performed by Mutalik *et al* (97) in patients with localized stable vitiligo treated with autologous nonculture melanocyte-keratinocyte cell transplant (NCMKT). The objective was to assess the efficacy of cyclosporine to prevent the perilesional depigmentation halo seen after NCMKT surgery. The treatment group received cyclosporine postoperatively for 3 weeks at 3 mg/kg/day followed by cyclosporine for 6 weeks at 1.5 mg/kg/day. The results were >75% repigmentation in 100% of patients in the cyclosporine group compared with 28% of patients in the group without treatment. In the latter group, most patients (52%) achieved 25-50% repigmentation. The authors concluded that postoperative cyclosporine allowed a uniform and complete repigmentation following NCMKT (97).

The side effects of cyclosporine are renal dysfunction, hypertension, gingival hyperplasia, hypercalcemia, hyperuricemia, nausea, abdominal discomfort, tremor, headache, arthralgias and hypertrichosis (24,96).

Mycophenolate mofetil (MM). MM inhibits *de novo* purine synthesis in T and B lymphocytes through inhibition of the enzyme inosine-5' monophosphate dehydrogenase (98). Bishnoi *et al* (98) evaluated MM efficacy in stabilizing non-segmental vitiligo. Mofetil mycophenolate up to 1 g twice daily was compared with dexamethasone 2.5 mg on 2 successive days weekly for 180 days. The arrest of disease activity was achieved in 80% of patients in the corticosteroid group compared with 72% of patients in the MM group. The most common side effects in the MM group were nausea and diarrhea. Treatment was discontinued in two patients in the MM group due to leucopenia and transaminitis, respectively (98).

3. Physical therapy

Phototherapy

Narrow-band UVB. Ultraviolet radiation, more markedly UVB (wavelength of 280-320 nm) than UVA (wavelength of 320-400 nm), has several systemic effects, such as activation of the central hypothalamic-pituitary-adrenal axis, activation of the proopiomelanocortin pathway in the arcuate nucleus of the hypothalamus, immunosuppressor and opioidogenic effects (99-101). These effects are through upregulation of the local neuroendocrine axes (99-101). The mechanism of action of nb-UVB (wavelength of 311 nm) phototherapy in vitiligo is through immunosuppression, induction of melanocyte differentiation, melanin production and migration of melanocytes from perilesional skin (22,102). Total body nb-UVB is recommended for widespread vitiligo >15-20% of the body surface area and for rapidly progressive vitiligo (18).

Regarding phototherapy with nb-UVB, The Vitiligo Working Group recommends three sessions every week as an optimal frequency of administration (103). Regardless of the patients phototype, the initial dose is 200 mJ/cm^2 (103). Following a phototherapy session, pink erythema lasting less than 24 h is desired; if this does not occur, the dose can be increased by 10-20% each session until pink erythema is achieved (103). The same dose is held until erythema disappears, then once again the dosage is incremented (103). The response to treatment should be assessed after 18-36 sessions and because of the existence of slow responders, at least 72 sessions are recommended before discontinuing therapy (103). There is no maximum number of sessions in patients with phototypes IV-VI, and no recommendation was made for other phototypes (103). The maximum acceptable dose is 1,500 mJ/cm^2 for the face and 3,000 mJ/cm^2 for the body (103).

Treatment response to monotherapy with nb-UVB phototherapy was evaluated in a systematic review and meta-analysis by Bae *et al* (104), where ≥25% repigmentation was achieved in 62.1% of patients at 3 months, 74.2% of patients at 6 months and 75% of patients at 12 months. In addition, >75% repigmentation was observed in 13, 19.2 and 35.7% of patients at 3, 6 and 12 months, respectively. According to the site, the best response was observed on the face and neck, followed by the trunk, extremities, and lastly the hands and feet (104).

In a meta-analysis performed by Lee *et al* (28), a combination of nb-UVB or excimer laser (EL) with TCI exhibited a mild response (≥25% repigmentation) in 89.5% of patients, a moderate response (≥50% repigmentation) in 72.9% of patients and a marked response (≥75% repigmentation) in 47.5% of patients. The authors suggest that this combination has a synergistic effect (28). In another meta-analysis by Li *et al* (105), the benefit of nb-UVB combined with topical D3A, or nb-UVB combined with TCI compared to nb-UVB alone was investigated, where no significant superior effect was observed in the combined therapy group (105). However, this meta-analysis revealed that combining TCI and nb-UVB may improve the clinical response in the face and neck (105). The combination of nb-UVB with systemic therapies includes the study by Tovar-Garza *et al* (106), evaluating the efficacy of oral mini-pulse of dexamethasone 4 mg on 2 consecutive days weekly with nb-UVB and topical clobetasol compared with nb-UVB and topical clobetasol. A total of 92% of patients achieved disease arrest with dexamethasone, nb-UVB and clobetasol, compared with 53% of patients with nb-UVB and clobetasol (106). In a meta-analysis, Phan *et al* (107) studied the effectiveness of JAK inhibitors used with UVB phototherapy; improved efficacy was reported with the combination of both treatments. A good response was observed in 11.1% of patients receiving JAK inhibitor alone, compared with 88.9% of patients with concurrent phototherapy (107). Khemis *et al* (108) evaluated efficacy using apremilast 30 mg twice daily in combination with nb-UVB compared with placebo and nb-UVB in 80 patients. Apremilast combined with nb-UVB did not exhibit an additional benefit in repigmentation compared with nb-UVB alone (108). Lim *et al* (109) performed a randomized control trial of nb-UVB alone compared to afamelanotide 16 mg subcutaneously applied monthly for 4 months along with nb-UVB. The results demonstrated repigmentation response of 48.6% in the combination therapy group compared with 33.26% in the nb-UVB monotherapy group at day 168 (109). In a meta-analysis, Chang *et al* (110) evaluated the efficacy of combining nb-UVB with fractional CO_2 laser, but no additional benefit in repigmentation was observed. The adverse reactions of nb-UVB include burning, erythema, pruritus, xerosis, photoaging and photodamage (47).

PUVA. PUVA radiation (wavelength of 320-340 nm) induces melanogenesis by immunosuppression and promoting a favorable milieu for the growth of melanocytes (18,111). This treatment, considered a second-line therapy, requires topical application or ingestion of psoralen and exposure to UVA (18). The oral psoralens are given 1-3 h before the UVA radiation, some examples are 8-methoxypsoralen (0.6-0.8 mg/kg), 5-methoxypsoralen (1.2-1.8 mg/kg) and trimethylpsoralen (0.6 mg/kg) (18). Topical PUVA uses the psoralen as a cream or ointment (8-methoxypsoralen 0.001%) and is applied 30 min before UVA radiation. The advantages of topical PUVA include fewer treatments, smaller cumulative UVA doses, less systemic and ocular phototoxicity (18). PUVA therapy should be given for at least 6 months before considering the patient non-responsive and for a maximal response, continuous therapy is required for up to 1-2 years (18). Efficacy of PUVA phototherapy reported by Bae *et al* (104) in a systematic review and meta-analysis was ≥25% repigmentation in 51.4% of patients at 6 months and 61.6% of patients at 12 months; ≥75% repigmentation in 8.5% of patients at 6 months and 13.6% of patients at 1 year (104). Parsad *et al* (112) compared treatment with nb-UVB to PUVA and marked to complete repigmentation was observed in 41.9% of patients with nb-UVB compared

with 23.6% of patients with PUVA. Bhatnagar *et al* (113) compared treatment for induction of stability with nb-UVB or PUVA; vitiligo was arrested in 80% of patients using nb-UVB and only 40% of patients with PUVA. The side effects of PUVA are phototoxicity, headache, dizziness, depression, insomnia, hyperactivity, bronchoconstriction, tachycardia, ankle edema, nausea, vomiting, pruritus, xerosis, photoaging, hyperpigmentation, hypertrichosis, increased risk of non-melanoma skin cancer, and liver and eye toxicity (114,115).

Laser therapy

EL. Excimer light (wavelength of 308 nm) in excimer lamps and EL are useful for targeted phototherapy (116). The mechanism of action is a direct cytotoxic effect on T cells, and stimulation of melanocyte migration and proliferation in hair follicles (117). In a systematic review and meta-analysis by Lopes *et al* (118) no significant difference in efficacy was observed between excimer lamps, EL and nb-UVB in achieving ≥50 and ≥75% repigmentation. In a systematic review and meta-analysis, Bae *et al* (119) reported that the combination of excimer laser/EL and TCI were more effective than monotherapy with EL, also the treatment failure rate was reduced with the combination therapy (119). The side effects of EL are pruritus, burning sensation and dryness (118).

Combined Fraxel Erbium and UVA1 laser. Lotti *et al* (120) investigated a combined laser and topical latanoprost approach in 30 adults with vitiligo, with active or stable localized disease. Initially, the vitiliginous lesions were treated with a single passage of Fraxel Herbium laser, with a wavelength of 1,540 nm and an energy level of 1,800 mJ/P. Immediately after obtaining columnar areas of epidermal ablation, they applied latanoprost 0.005% solution onto each skin lesion. After 24 h, the skin lesions were irradiated with a UVA1 laser (355 nm) for 20 min. The treatment was repeated every 21 days, for 9 months. A total of 27 patients (90%) obtained >75% repigmentation, while three patients (10%) achieved 50-75% repigmentation (120).

4. Depigmentation therapies

These therapies are generally recommended for extensive and refractory vitiligo, when >50% of the body surface is affected or if cosmetically sensitive areas are the major component involved (18,19). Monobenzyl ether of hydroquinone (MBEH) 10% is applied topically daily the first month, then MBEH 20% is applied daily for 1 month, and after that twice daily. The concentration can be increased to 30-40% if the areas are unresponsive, if tolerated. In general, patients present depigmentation after 3-6 months in areas distal to the application (19,121). Other treatment options are 4-methoxyphenol, 88% phenol solution, laser and cryotherapy (121).

5. Conclusions

Vitiligo treatment can sometimes be frustrating due to the inconsistency in clinical improvement and its relapsing feature. Therapy should be individualized according to the type of vitiligo, presence of activity and the side-effect profile of the drug used. All therapies for vitiligo are limited, no known treatment can consistently produce repigmentation in all patients. Further basic and clinical investigation is required to better understand the pathogenesis of vitiligo and provide new targets for therapy. There are multiple upcoming therapies, and most information of these new treatments are case reports or series. However, more randomized controlled trials are required to better evaluate their efficacy.

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JOC, DEKL, NAZS, SLSF, CNSD, MASS, HGMR and OTVM performed the literature review and collected the data. JOC, DEKL, NAZS, SLSF, CNSD, MASS, HGMR and OTVM drafted the initial manuscript. JOC, DEKL, NAZS, SLSF, CNSD, MASS, HGMR, OTVM, UW and TL improved the manuscript. JOC, DEKL, NAZS, SLSF, CNSD, MASS, HGMR, OTVM, UW and TL critically revised the manuscript for important intellectual content. Data sharing is not applicable. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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