Expert Opinion on Emerging Drugs

ISSN: 1472-8214 (Print) 1744-7623 (Online) Journal homepage: https://www.tandfonline.com/loi/iemd20

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To cite this article: Aleksandra Vojvodic, Priyanka Karagaiah, Yan Valle, Julia Sigova, Nicola Zerbinati, Petar Vojvodic, Davinder Parsad, Robert A. Schwaertz, Stephan Grabbe, Mohamad Goldust & Torello Lotti (2020): Emerging drugs for the treatment of vitiligo, Expert Opinion on Emerging Drugs, DOI: 10.1080/14728214.2020.1712358

To link to this article: https://doi.org/10.1080/14728214.2020.1712358

Accepted author version posted online: 20 Jan 2020.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Opinion on Emerging Drugs*

DOI: 10.1080/14728214.2020.1712358

Emerging drugs for the treatment of vitiligo

Aleksandra Vojvodic[1], Priyanka Karagaiah[2], Yan Valle[3], Julia Sigova[4], Nicola Zerbinati[5], Petar Vojvodic[6], Davinder Parsad[7], Robert A. Schwaertz[8], Stephan Grabbe[9], Mohamad Goldust[10], Torello Lotti[11,*]

1. Military Medical Academy of Belgrade, Belgrade, Serbia

2. Department of Dermatology, Bangalore Medical College and Research Institute, Bangalore, India

3. Vitiligo Research Foundation, New York, New York, United States

4. Pirogov Russian National Research Medical University, Moscow, Russia

5. Universita degli Studi dell'Insubria Dipartimento di Scienze Chirurgiche e Morfologiche, Varese, Italy

6. Clinic for Mental Disorders "Dr Laza Lazarevic", Belgrade, Serbia

7. Department of Dermatology, PGIMER, Chandigarh, India

8. Dermatology, Rutgers New Jersey Medical School, Newark, New Jersey, United States

9. Department of Dermatology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

10. University of Rome Guglielmo Marconi, Rome, Italy, Department of Dermatology, University Medical Center Mainz, Mainz, Germany

11. Professor of Dermatology, University of Studies Guglielmo Marconi, Rome, Italy

***Correspondence**

Torello Lotti

Email: Professor@torellolotti.it**;** Phone**:** +393286214588; Fax: +390637725647

Abstract

Introduction: Vitiligo is a relatively common autoimmune depigmenting disorder of skin. There has been a great advance in understanding the pathological basis, which has led to development and utilisation of various new molecules in treating vitiligo. This review aims at a comprehensively describing the treatments available and the emerging treatment aspects and the scope for future developments.

Areas covered: This study comprehensively summarises the current concepts in the pathogenesis of vitiligo with special focus on the cytokine and signalling pathways, which are the targets for newer drugs. JAK kinase signalling pathways and the cytokines involved are the focus of vitiligo treatment in current research, followed by antioxidant mechanisms and repigmenting mechanisms. Topical immunosuppressants may be an alternative to steroids in localised vitiligo. Newer repigmenting agents like basic fibroblast growth factors, afamelanotide have been included and a special emphasis is laid on the upcoming targeted immunotherapy.

Expert opinion: The treatment of vitiligo needs to be multimodal with emphasis on targeting different limbs of the pathogenesis. Topical and oral JAK inhibitors are the most promising new class of drugs currently available for treating vitiligo and acts best in conjunction with NB-UVB.

Key words: Biologics, JAK inhibitor, Treatment**,** Vitiligo

1. Background

Vitiligo is an acquired autoimmune disorder characterized by well circumscribed, sharply demarcated, depigmented confluent macules and patches resulting from progressive loss of epidermal melanocytes affecting nearly 0.5–2% of the world's population [1, 2]. An analysis of several hospital-based studies revealed a higher prevalence of vitiligo amongst the African population (2.5%) as compared to 1.5% in American and 1.6% in Asian population [3].

Though the onset of disease peaks around 10 - 30 years of age, it can occur anytime during an individual's lifetime. The prevalence is shown to increase with age, probably due to the cumulative effect as vitiligo has a long-standing course with unsatisfactory response to treatment. Both sexes have shown almost equal prevalence. It is known to affect all races equally [2, 3]. Family history is noted in 15 to 20 % of the cases and associated with earlier onset of disease, especially in consanguineous marriages. Large cohorts have demonstrated association of vitiligo with other autoimmune disorders like thyroid disease, type 1 diabetes mellitus, lichen planus, alopecia areata, psoriasis and atopic dermatitis [4].

The etiopathogenesis of vitiligo is multifaceted with a complex interaction between the genetic and nongenetic factors. Large number of susceptibility genes have been identified by Genome Wide Association Studies (GWAS) [5].

The recruitment of cells of innate immunity such as the natural killer (NK) cells, cytokines like IL-1β, IL6, and IL-8 in abundance following any insult to the microenvironment of the melanocyte, non-selectively target the stressed melanocytes. Inducible Heat Shock Protein 70 (HSP70i) acts as link between innate and cellular immunity.[6,7]. This further sets off a cascade of melanocyte destruction by the mature cytotoxic CD8 T lymphocytes and JAK STAT intracellular signalling pathways plays a major role in chemokine (IFN γ, IL 15, CXCL 10) mediated recruitment of these cells to the epidermis and maintenance of disease progression [8,9].

Oxidative stress has an important role to play in free radical mediated destruction of melanocyte [10,11]. Although many such mechanisms have been proposed, the pathogenesis is still not completely understood, posing a problem in selection of treatment modalities.

Clinically the lesions can be categorised into segmental (SV) and non-segmental vitiligo (NSV). Segmental vitiligo presents as a focal, dermatomal patch with rapid progression and often associated with leukotrichia. Neural mechanisms were proposed as the probable cause, as segmental vitiligo was believed to follow a dermatomal distribution and several studies have also reported increased neuropeptide release (e.g., neuropeptide Y) in the lesional skin. However, segmental vitiligo need not necessarily follow a dermatomal distribution and more often overlap with the pattern of segmental lentiginosis. Currently, somatic mosaicism and subsequent inflammatory reaction leading to melanocyte destruction is the most plausible theory. [12]

Non segmental type has various subtypes like acral, acrofacial, mucosal, vulgaris and generalised vitiligo, often distributed symmetrically. Occasionally there can be mixed type with both segmental and nonsegmental vitiligo in the same patient [13].

The treatment modalities are largely comprised of off label, non-specific immunosuppressants with moderate efficacy and remission induced is short lasting with frequent recurrences. The treatment depends on the disease stability and extent of body surface area involved and has to be individualised to the needs of the patient. The first step is aimed at stabilisation of the disease process. In stable cases, the focus is on melanocyte stimulation to induce repigmentation of the patches [14].

2. Medical need

The disease is not just a cosmetically disfiguring problem but also has a grave psychological burden on the patient as well as the family. However, there has been increasing awareness regarding the disease, the societal paradigm of an ideal skin colour and appearance has made it far more disfiguring than it actually is. In addition to the disease per se, long treatment duration along with uncertainty of treatment

success and frequent recurrences have dampened the quality of life in terms of self-esteem and emotional wellbeing significantly in affected individuals [15].

The diverse array of therapeutics available for unstable disease pose a problem to the treating physician owing to the nonspecific nature of the immunosupressants, with modest efficacy and potential side effects with long-term usage. Rapid growth in the field of research has given scope for developing new drugs targeting a specific immune system pathways and molecules and thereby halting the progression of the further melanocyte destruction and may be even stimulate pigment production by the melanocytes.

Even with rapid development the lack of uniform guidelines for treating and standardisation of outcome measures, posed a problem in analysing the scientific evidence previously. Recently, an image based uniform scoring system for both marginal and perifollicular repigmentation with good inter-rater variability has been developed by the Bae J et al and may serve as a reliable assessment model of treatment response in vitiligo. [16]

Prevention of recurrence, once a farfetched goal now seems plausible owing to discovery of cellular targets that can modify the memory T cells as shown by animal models. This is of particular interest as it provides scope for development of potential novel drugs that can benefit the patient in true sense.

3. Existing treatment

Current treatment options can be broadly classified into medical and surgical modalities (Figure 1). Medical line of treatment can further be divided into topical, systemic and phototherapy.

As per European Dermatology Forum consensus guidelines, first line of treatment for segmental vitiligo comprises of topical corticosteroids / topical calcineurin inhibitors along with inhibition of triggering factors and camouflage for better cosmetic appearance. After the stabilisation of the disease, surgical modalities can be considered if repigmentation is not achieved. If stability is not achieved targeted phototherapy can be used to halt the progression and also to induce pigmentation.

For non-segmental vitiligo involving large areas NB – UVB has to be tried for at least 3 months to achieve stability before changing onto systemic corticosteroids/ other immunosupresssants in case of no response. Maintenance therapy has to be given for at least 9 months in responsive cases and may be combined with topical agents for synergistic effect. In non-responders with > 75% of body surface area involvement depigmentation can be tried using monobenzone. [17]

3.1 Topical medications

3.1.1 Topical corticosteroids

Corticosteroids act by local immunomodulation and also stimulation of melanocytes for pigment production in the affected akin. They mainly act by binding to the glucocorticoid receptor pigment (GC receptor) and reducing the gene expression of large number of cytokines like IL-1, IL-2, IL-3, IL- 4, IL-5, IL-6, IL-8, IL-10, IL-13, GM-CSF, TNF-α and interferon-γ

And thereby inhibiting the activation of cytotoxic T lymphocytes. It is also known to reduce B cell responses against the self-antigens. [18]

A meta-analysis of nonsurgical treatment in vitiligo has shown class Ⅲ and class Ⅳ corticosteroids to be effective in treating non-segmental vitiligo with 40 to 56% of patients achieving > 75% repigmentation [18]. Although, clobetasol propionate and betamethasone valearate used in different concentrations have shown good efficacy, they are associated with significant local side effects on long term use [18,19]. Mometasone on the other hand has similar efficacy but with the advantage of lesser side effects and good safety profile in both adults and children [20]. Fluticasone propionate in combination with UV-A yielded better results than alone in a comparison study [21]. Topical corticosteroids may be slightly more superior to calcineurin inhibitors in efficacy and work best in combination than with monotherapy. [22]

Atrophy, telangiectasia, hypopigmentation, straie, folliculitis, acneiform eruptions are few well known side effects of topical corticosteroids especially with high potency corticosteroids like clobetasol. But mometasone and fluticasone can be safely used in extrafacial areas, intermittently for limited time periods. Systemic absorption and

suppression of hypothalamic pituitary adrenal (HPA) axis may be a concern if large area is involved and in children when potent steroids are used for long durations [17].

3.1.2 Topical calcineurin inhibitors

Topical calcineurin inhibitors have an immunomodulatory effect on the cytotoxic T cells by inhibiting the IL-2 and IFN – γ [13, 23] and tacrolimus has also been shown to reduce systemic antioxidant stress [24] that brings about disease control and repigmentation in vitiligo.

In a double blinded randomized controlled trial (RCT) by Lubaki et al., tacrolimus had better repigmentation rates compared to placebo, especially on the face and upper back, with pigment appearing within the 1st four months of treatment [24]. A double blinded RCT showed superior efficacy with tacrolimus 0.1% ointment compared to clobetasol 0.05% when assessed by computerized morphometric analysis, although no significant difference was noticed by clinical evaluation [25]. In an open label study of 110 patients 40% of patients demonstrated repigmentation greater than 75% on the face as compared to 21.5% on the trunk, 23% on the extremities and only 1% on the hands and feet [26]. Pimecrolimus on the other hand showed mixed results with no difference in repigmentation [27] and was inferior to clobetasol [28] when used on non-facial lesions but has good efficacy in facial lesions as revealed by many open studies [28,29].

Tacrolimus worked well in conjunction with excimer laser with greater than 75% repigmentation in resistant sites, such as extremities and bony prominences, in 60% of patients ($P < 0.002$) [30]. Likewise, single-blind studies on combination of pimecrolimus with 308-nm excimer have revealed superior pigmentation in comparison to excimer laser monotherapy for facial lesions [31]. Tacrolimus and pimecrolimus have showed better results when given with NB-UVB. Tacrolimus 0.1% ointment showed a median reduction of 42.1% compared to 29% on the placebo ointment when irradiated with NB-UVB in a left right comparison randomised control trial. It was observed that cumulative dose of tacrolimus correlated with repigmentation ($P = 0.044$) [32]. Evidence has shown superiority of pimecrolimus over placebo when combined with NB-UVB especially over facial lesions [27].

Topical CIs are generally safe with occasional side effects like pruritis, erythema and burning and are devoid the side effects of topical corticosteroids like atrophy and telangiecatasia. Thus it can be safely used in sensitive areas like the face, neck and intertriginous areas and in children for long durations when used intermittently [13,24,25].

3.1.3 Topical Vitamin D analogues

Calcipotriol 0.005% ointment as a monotherapy has not been satisfactory [33] in treating vitiligo in adults but has shown a moderate response with 50 to 75% repigmentation in children [34].

Few studies have suggested that calcipotriol has no additional role in repigmentation when combined with NB-UVB and may also dampen the onset of pigmentation [35,36]. While few studies have noticed higher response rates when combined with NB-UVB and PUVAsol with a faster and sustained response obtained in fewer sessions [36,37].

Combination of calcipotriol 0.005% and betamethasone dipropionate 0.05% has shown mild to moderate response (25 – 75% pigmentation) in unstable vitiligo and well tolerated by the patients [38].

3.1.4 Topical prostaglandin analogues

Hyperpigmentation of periocular skin while treating glaucoma prompted the use of topical prostaglandin analogues in vitiligo. They are known to induce tyrosinase and upregulate melanocyte proliferation [39].

An open label study comprising of 56 patients treated with topical PG- E2 gel showed promising results with complete pigmentation in 6 facial and 2 non facial lesions and excellent repigmentation (>75% repigmentation) in 22 patients [39].

Latanoprost was found to be superior to placebo with >50% repigmentation in 42.9% of cases vs. 0% lesions in placebo, at 6 months and was also comparable to NB-UVB in efficacy. In addition, combination of latanoprost and NB-UVB was superior to NBUVB (62.5% vs. 12.5% repigmentation) after treating for 6 months [40]. Another

trial with 0.03% solution of topical bimatoprost with twice a day application in facial vitiligo, in children, observed excellent repigmentation (> 75%) in 4 out of 8 patients, after 12 weeks [41]. Another randomised control trial in non-facial vitiligo showed at least 46% of the bimatoprost plus mometasone group showing 50 to 75% repigmentation compared to 18% in the bimatoprost monotherapy group, and 0% in the mometasone plus placebo group, at 20 weeks [42]. Authors concluded that prostaglandin analogues are better suited for treating periocular vitiligo and disease of lesser duration. Side effects were limited to mild irriation and burning [39,40].

3.1.5 Topical antioxidants: Catalase and superoxide dismutase

Colucci et al. stated that antioxidants, can be used in association with other therapeutic options [43].

A case study of 33 patients concluded combination of topical pseudocatalase/calcium with short-term NB-UVB therapy to be remarkably effective in inducing repigmentation on the face and dorsum of the hands [44] while other studies failed to confirm the same [45,46]. A prospective study with 59 patients undergoing Dead Sea climatotherapy showed faster initiation of pigmentation within 10 to 16 days and had greater activation of pseudocatalase enzyme in the treated skin, with reduction in H2O2 levels when combined with topical pseudocatalase, compared to either of the modality as monotherapy [47].

3.2 Phototherapy

Phototherapy being an immunomodulator and inducer of melanocyte proliferation is considered the first line of treatment in vitiligo with involvement of body surface area greater than 10%, with special place in treatment of children.

3.2.1 PUVA- Psoralen plus UVA

A light source comprising of broad band UVA (320-380nm) along with either oral or topical psoralen is given after determining the minimal phototoxic dose and incremented at 0.5 to 1.5 J/cm^2 till the maximum tolerable dose is reached. It acts by

activating follicular melanocytes and release of keratinocyte growth factors that promote melanocyte growth [48].

A meta-analysis of prospective studies of phototherapy showed marked response (75% repigmentation) to PUVA in 8.5% and 13.6% of patients, at 6 months and 12 months respectively and mild response in 51.4% at 6 months and 61.6% at 12 months. The response was 78%- 100% for head and neck lesions, and was mostly resistant at acral sites and mucosa. Darker skin type responded better to the treatment [49]. Relapse has been noticed in upto 75% of the cases treated with PUVA, within 1 to 2 years.[17]

Topical 8-methoxypsoralen psoralen having the benefit of lack of systemic side effects such as nausea, vomiting, central nervous system (CNS) side effects such as headache, dizziness, depression, insomnia and hyperactivity, bronchoconstriction, drug fever, tachycardia, ankle oedema, hyperpigmentation of normal surrounding skin etc., is preferred over systemic psoralen [Oral 8-MOP(0.5-0.8mg/kg bw)] in patients with < 5% BSA involvement. Topical treatment is associated with local phototoxic reaction like erythema, blistering, burning sensation and rarely ulceration, especially with 5- MOP and trimethoxypsoralen. Long-term side effects included liver toxicity, photoaging, eye toxicity and risk of cutaneous non melanoma malignancies [48].

3.2.2 Narrow band UV-B (NB-UVB)

NB-UVB with its peak emission at 311 nm acts by inducing tyrosinase enzyme and increasing the expression of HMB45 on the melanosome surface [13]. NB-UVB has taken over PUVA in the last decade. Yones et al. demonstrated higher number of patients (64%) showing more than 50% repigmentation after 6 months of treatment with NB-UVB than in the PUVA group (36%). Excellent colour match was noted in all patients in the NBUVB group but only 44% had good colour match in PUVA group [50].

A meta-analysis demonstrated marked response (≥75%repigmentation) in 35.7% and moderate response (≥50% repigmentation) in 56.8% after 12 months of NBUVB phototherapy. Authors are of the opinion that a minimum of 6 months is required for treatment to be successful and ideally be given for at least one year as 62.1% of

patients showed at least a mild response (≥25% repigmentation) within 3 months. As per the analysis, face and neck were the most responsive sites with marked repigmentation rate in 44.2% of cases, followed by the trunk (26.1%). Extremities were the least responsive with acral sites being almost completely resistant to treatment [49]. Relapse was seen in 21% to 44% of cases within 1 year and 55% of cases within 2 years of NB-UVB treatment [17].

Better and faster results were seen in children, with average treatment required to achieve 50% repigmentation being 34 weeks [51]. Multiple studies have demonstrated superior efficacy of NBUVB over PUVA phototherapy in achieving disease stability and repigmentation. Side effects of NB-UVB include erythema, itching, and mild burning, which spontaneously resolve in few hours of treatment in most cases [49].

3.2.3 Other photochemotherapies

3.2.3.1 Khellin

Khellin is a furanochrome with a vasodilatory action that can stimulate melanogenesis on exposure to UV A light [13]. It is given orally at 50- 100 mg/kg bw, 45 minutes to 1 hour before exposure to UV light. Studies have shown up to 70% repigmentation rates in 41% patients, which was comparable to PUVA and with fewer side effects but required treatment for longer duration with higher doses [52,53]. However, topical khellin has been found to be ineffective when combined with either UV-A [54] or Monochromatic Excimer laser 308nm [55] in providing any additional benefit.

3.2.3.2 L Phenylalanine (L-phe)

Phenylalanine, an essential amino acid required for melanogenesis, is supplemented orally ideally 45 minutes prior to phototherapy for good repigmentation rates up to 50%-100% [55]. Camacho and Mazuecos evaluated oral and topical L-phe, clobetasol propionate, and UVA/sunlight--a new study for the treatment of vitiligo and demonstrated that L-phe in combination with 0.025% clobetasol propionate and

sunlight during sunny months or UVA lamps in winter, appears to improve evolutive vitiligo without side effects, and therefore is especially recommended on the face or for children[56]. Combination of topical L-phe with oral L-phe and light therapy was found to be even more beneficial [57].

3.3 Lasers

3.3.1 Monochromatic excimer laser (MEL)

The MEL 308nm laser is FDA approved for treating vitiligo. When used alone more than 75% repigmentation was reported in 20.7 % - 29 % of the patients [58]. Face responds best with average duration for onset of pigmentation being 11 days and poorly responsive in acral areas. MEL may have better clinical outcomes than NB-UVB and work better with combination with topical hydrocortisone and topical tacrolimus. However, MEL failed to show any additional benefits with topical vitamin D analogues and khellin [59].

3.3.2 Helium Neon laser

The helium neon (632.8-nm) (HeNe) laser has been tried in head and neck segmental vitiligo at biweekly intervals with 60% of patients showing greater than 50% repigmentation, beginning after 16 to 17 treatments [60].

3.4 Systemic treatment

3.4.1 Systemic corticosteroids

Systemic corticosteroids (CS), are second line of treatment in patients not responding adequately to topical medications and NB-UVB. A large study on 444 patients treated with low dose oral dexamethasone 2.5mg on two consecutive days in a week revealed disease stabilisation in 408 (91.8%) patients with some repigmentation achieved in all patients after a mean duration of 13.2 ± 3.1 weeks. Relapse was noticed in 12.25% patients with mean disease-free period being 55.7 ± 26.7 weeks. 41 (9.2%) patients complained of side effects like weight gain, acneiform eruptions and lethargy [61]. Similar results were found in other studies

[18]. As an adjuvant to phototherapy, oral pulse steroids achieved maximum repigmentation with NBUVB compared to PUVA [49].

In a one year follow up study, 138 children were treated with methylprednisolone pulse therapy for 6 months and observed that 34.8% patients had recurrence of lesions at the end of the study.[62]

3.4.2 Azathioprine

Azathioprine, a 6 mercaptopurine derivative, was tried in combination with PUVA, with mean repigmentation rate of 58.4% after 4 months in comparison to 24.8% with PUVA alone [63] 50 mg azathioprine given daily for 6 months was comparable in efficacy to betamethasone pulse therapy given for the same duration, although the onset of pigmentation was faster in azathioprine group [64].

3.5 Surgical methods

The hair follicle outer root sheath acts as a melanocyte reservoir, essential for the success of medical therapy. Surgical therapies aim at re-introducing the harvested melanocytes in the depigmented vitiliginous lesions.

Surgical procedures are of two types; tissue grafting and cellular grafting.

3.5.1 Tissue grafts

3.5.1.1 Split thickness skin grafts (STSG)

Behl first conducted Thiersch's skin grafting in 107 vitiligo patients and yielded excellent repigmentation in 70% of the patients, with milia being the most common side effect [65]. In another study, a total of 84 lesions in 40 patients were treated with ultrathin split-thickness skin grafting followed by NB-UVB, starting 10-15 days after the grafting. 83% of the patients achieved >90% repigmentation with mean duration to onset of pigmentation ranging from 7 to 18 days and observed excellent cosmetic matching in 90% of the grafted lesions. Face showed best results, with all patients

achieving >90% repigmentation followed by arms, abdomen, and back. Even resistant sites like elbows and breast lesions showed >90% repigmentation [66].

In a prospective study comparing punch grafting with STSG, 15 of the 34 patients receiving punch grafting therapy had excellent (> 75%) repigmentation when compared to 25 of 30 patients in the STSG group [67].

Perigraft halo, milia and graft displacement are the common recipient site adverse effects. Scarring and infection at the donor site are the commonest complications. Disadvantage of STSG is that it needs multiple sessions at 4 to 12 week interval in large lesions and may require general anesthesia when harvesting grafts from large areas and multiple sites [66].

3.5.1.2 Mini punch grafts

Malakar et al. evaluated 100 patients who were treated with mini punch grafting and observed 90% to 100% repigmentation in 74.5%, no repigmentation in 10.5%, and depigmentation in 2.3% of cases [68]. Complications included cobblestoning, colour mismatch and scarring at the donor site.

3.5.1.3 Blister roof grafts

In a retrospective review of 1100 patients with stable vitiligo, treated with blister roof grafting, an overall success rate of 72.3% was observed. 20.6% patients showed complete repigmentation and 51.6% showed > 50% repigmentation. Repigmentation was nil in only 3.9% of the patients after the treatment. 1.4 % of the patients showed recurrence of lesions within 6–12 months of treatment when followed up for 1–5 years. Lesions on the face, neck and extremities showed better response than those at other sites [69].

In a prospective comparative study, excellent results (>75% repigmentation) was observed in 66.67% of patients compared to 48% in punch grafting and 40% in split thickness after 6 months and suction blister group had the fastest repigmentation rates and least side effects making it a preferable choice amongst the tissue grafts [70].

3.5.2 Cellular grafts

The essence of cellular grafts is to harvest viable tissue from the pigmented normal site through either of the methods – punch grafting, blister roof grafting, curettage, or STSG and separate the individual cells of the epidermis to form a suspension, and then transfer them onto de-epithelialized recipient vitiliginous skin. Techniques include melanocyte only transplantation or both keratinocytes and melanocytes transplantation or follicular epidermal cell suspension transplantation. Cell culturing is also used to obtain large number of viable cells from less donor tissue [13].

In a five-year follow up study, 49 patients with segmental vitiligo and 15 patients with focal vitiligo were treated with noncultured melanocyte-keratinocyte cell transplantation. In segmental vitiligo group, 84% of patients showed excellent response and 10% of patients failed to show any repimentation, with up to 13 patients retaining pigment at the end of 5 years. In focal vitiligo group, 73% showed an excellent response and 20% had poor results at the end of the study and only 3 patients retained pigment at the end of 5 years [71].

In another large study, 120 patients of stable localized vitiligo treated with autologous cultured melanocyte transplantation after carbon-dioxide laser abrasion, showed excellent repigmentation (90% to 100%).[72] But it requires a well-equipped laboratory for culturing cells and takes longer time compared to non-cultured methods, but has the advantage of covering larger areas with small donor tissue harvest. Side effect profile was similar to non-cultured melanocyte transplantation.

Outer root sheath melanocyte suspension prepared by follicular unit extraction was transplanted over dermabraded recipient area and pressure dressing was done in 25 patients in a prospective study. Excellent repigmentation (90-100%) was noted in 60% of patients with a mean repigmentation rate of 80.15% ± 22.9%. This method proves to be simple, safe, minimally invasive and effective and associated with less scarring of donor area [73]. This was comparable to noncultured autologous epidermal cell suspension transfer [74].

3.6 Depigmenting treatment

In extensive vitiligo, not responding to treatment and where the sites of normal pigmentation may cause cosmetic disfigurement, various depigmenting treatments are used to get a uniform depigmentation.

Monobenzyl ether of hydroquinone (MBEH) is the only US FDA approved agent and is commonly used. MBEH acts by inducing cellular oxidative stress and lysosomal degradation of melanosomes by autophagy which exposes the tyrosinase and MART-1 antigen containing exosomes, thereby triggering the immune response [13].

Q-switch Ruby and Q-switch Alexandrite lasers have also been used in depigmenting especially for larger areas. However, the major disadvantages are pain and availability of lasers [13].

4 Market review

Global market of vitiligo treatment as of 2018 was at 1243.8 million USD and is expected to reach a 1944.5 million USD by 2026, with a Compound annual growth rate (CAGR) of 5.8%. The largest share of the market at 54.7 % is attributed to topical medications with second largest share occupied by phototherapy followed by surgical methods and others. US has the largest market with 314.1 million USD in the vitiligo research and development pipeline and the largest growth rate is expected in the region of Asia Pacific owing to the growing pool of patients and increasing awareness about the vitiligo treatment.

The major factor hindering the growth of therapeutics previously was low to moderate efficacy, nonspecific therapeutics with low safety profile, long duration of treatment, recurrences and unmet needs of the patient. With the growing focus on targeted immunotherapy, the R&D aims at developing better molecules and thus, the global market is expected to grow bigger with key players in the market being Incyte Corporation, Pfizer, Baxter international Inc., Dr Reddy’s Laboratories and few others.

5 Current research goals

There has been a significant progress in the understanding the pathogenesis of vitiligo at a molecular and genetic level with greater focus on the intracellular environment and interplay of cytokines and signalling pathways.

Targeted immunotherapy currently is the centre of R&D pipeline followed by other strategies like melanocyte regeneration and reduction of microenvironmental oxidative stress.

Goals of treatment:

- Achieving longer duration of disease stabilisation and prevent recurrences.
- Development of effective drugs with a good safety profile.
- Achieving excellent repigmentation and cosmetic matching of the depigmented areas.
- Patient satisfaction

Key strategies in treatment of vitiligo currently include:

- Targeting Melanocyte stress – antioxidants.
- Targeted Immunotherapy – interfering with cytokine functions and cytokine signalling.
- Facilitating melanocyte regeneration and repigmentation

6 Scientific rationale

Vitiligo is multifactorial autoimmune disorder with complex pathogenetic mechanisms involved in melanocyte destruction and resultant depigmentation, Numerous susceptibility genes encoding both innate (NLRP1, CASP7, TRIF, C1QTNF6) and adaptive immunity (FOXP3, CCR6, PTPN22, IL2R, HLA class I and II) have been identified in large Genome wide association studies [75].

One major factor required for initiation of melanocyte destruction is the intrinsic defect in the oxidative stress coping mechanism in the native melanocytes. Studies have revealed elevated H_20_2 and decreased catalase and glutathione peroxidase, in the perilesional skin of vitiligo patients. Recent studies have revealed impaired Nrf2 pathway contributing to vulnerability of melanocytes to oxidative stress. [44,73]
The elevated H2O2 levels are responsible for recruitment of calreticulin (CRT) that induce expression of cytokines like IL-1β, IL6, IL-8, TNF-α, IL-6, IL-23, Monocyte Chemoattractant Protein (MCP)-1 etc. NF-kB acts a crucial mediators of inflammation and helps in production of cytokines such as TNF-α, IFN-γ, IL-6, IL-8, IL-1β, IL-23, IL-17 by inducing gene transcription of these cytokines. Cytokine imbalance has played a crucial role in development of vitiligo. [76]

Recent studies have demonstrated the presence of atypical mi-RNA (miR) expression in the skin and blood of vitiligo patients. Cytokines can induce the expression of miR-155 in melanocytes and keratinocytes, which when overtly expressed can inhibit expression of genes related to melanogenesis and melanocyte differentiation (SOX10, TYRP1, YWHAE, SDCBP). IL1B , IL1R1 and PTPN22 are the possible targets of different mi-RNAs all of which has been implicated in the pathogenesis of vitiligo. miR-211 produced by dendritic cells and macrophages is known to target IL23A and CHOP, both of which are expressed in high titres in the lesional skin of vitiligo patients. Thus, miRNAs may collectively influence melanocyte destruction and further disease progression in vitiligo by regulating the cytokine signalling. [77]

Inducible Heat shock protein 70 (HSP70i) is found to act as a link between innate and cellular immunity by recruiting melanocyte specific antigen presenting dendritic cells [78]. HSP70i induced elevation of pro-inflammatory cytokines like TNF- □, IL-1β, IL- 6, and IL-12 helps in dendritic cells maturation. Swine and mouse model studies have shown depigmentation reversed by modified Hsp70iQ435A and may open doors for new treatment potential in vitiligo [79].
Cytotoxic CD8 T lymphocytes are final effectors of melanocyte destruction in vitiligo. Recruitment of CD8 T lymphocytes is mediated by JAK-STAT intracellular signalling which mainly brings about upregulation of chemokine CXCL 10 and CXCR3 receptors in the keratinocytes. JAK, a transmembrane protein kinase is activated by extracellular binding of IFN-γ followed by self-phosphorylation and mediate the

formation of STAT protein dimers. This further activates nuclear transcription of CXCL 9 and CXCL 10 required for recruitment of cytotoxic T lymphocytes [80]. Recent studies have demonstrated the role of IL-15 in recruitment of CD8 T lymphocytes via JAK-STAT signalling pathway [81].

An in vitro study reported that HMG-CoA reductase inhibitor statins, which lower cholesterol, also inhibited STAT1 function. Another mouse model study has reported halting of disease progression and repigmentation following systemic simvastatin treatment [82].

FoxP3, a marker of Tregs (T cell regulatory cells) downregulates T cell activation and upregulates immunosuppressive molecules like CD25, CTLA-4. Studies have demonstrated significantly reduced number of FoxP3 positive Treg cells and CCL22, a Tregs homing receptor in lesional skin [78]. Tregs transfer, restoration of FoxP3 expression (i.e., vitamin D), Tregs enhancers (i.e., rapamycin) and topical CCL22 may be the new therapeutic approaches to be explored in future to halt the disease process [78].

Immune checkpoints Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4) and Programmed cell death protein 1 (PD-1) modulate T cell responses to inflammation. Immune checkpoints inhibitors in melanoma has paved way for exploring the possible role of Immune checkpoint dysregulations in vitiligo [84]. Selective stimulation of these checkpoints could restore immune tolerance and balance cytokine mileu in vitiligo [85].

7 Emerging treatment and competitive environment

7.5 Systemic immunomodulators

7.5.1 Minocycline

Minocycline, an antibiotic with immunomodulatory and anti-inflammatory properties has recently been tried in active vitiligo patients owing to its inhibitory action on free radical generation and cytokine production, interference with protein synthesis, potent antiapoptotic properties and modulation of matrix metalloproteinases. In a RCT, 100mg oral minocycline taken daily for six months was comparable to oral mini pulse corticosteroids in halting the disease activity [86]. Some side effects like nail,

skin, mucosal pigmentation, photosensitivity and nausea may be seen and has the disadvantage of taking drugs daily and may hamper the compliance.

7.1.2 Methotrexate

Methotrexate is an antimetabolite and anti-folate drug that is time tested in many autoimmune diseases and is safe when given for long duration. It helps in decreasing the number of T cells producing TNFa and thus may help in vitiligo.

A prospective randomized open label showed oral methotrexate 10mg weekly dose to be comparable to corticosteroid oral mini pulse (total weekly dose of 5 mg dexamethasone) after 6 months of treatment and was well tolerated. Sun exposed lesions responded the most and lesions on palms, soles and mucosa responded poorly to methotrexate. Blood parameters need to be closely monitored, as methotrexate is known to cause myelosuppression and hepatotoxicity.[87]

7.1.3 Cyclosporine

Cyclosporine, an oral calcineurin inhibitor interferes with interleukin‐2 production by inhibiting NFAT, a transcription factor necessary for transcription of genes encoding (IL‐2). IL 2 is a key cytokine mediating influx of lymphocytes and inhibiting it may be a therapeutic choice in patients with vitiligo.

A recent study by Taneja et al. demonstrated a statistically significant reduction in Vitiligo Area Scoring Index (VASI) score after treating 18 patients with oral cyclosporine (3 mg/kg/day), in two divided dosages for 3 months. Thus, cyclosporine was also capable of inducing repigmentation probably through its direct effect on melanogenesis, along with halting disease progression. Although well tolerated, it is associated with side effects like renal dysfunction, hypertension, hyperkalemia and gingival hyperplasia [88].

7.2 JAK-STAT inhibitors

7.2.1 Tofacitinib

Oral JAK 1/3 inhibitor tofacitinib 5mg twice daily has been reported to achieve complete re-pigmentation of depigmented lesions on the face and hands in a case of generalised progressive vitiligo after treating for 5 months [89]. In another case series of 10 patients, 5 patients responded with some repigmentation when treated with oral tofacitinib and all of them had received either adequate sun exposure or low dose NBUVB [90]. In a multicentric retrospective observational study of 67 patients with vitiligo, 9 patients with concurrent rheumatoid arthritis were given oral tofacitinib 10mg/day along with micro focussed narrow band UV- B (NBUVB) and other 58 patients were treated with NBUVB alone. Tofacitinib group of patients achieved excellent results (92% repigmentation), whereas NBUVB alone group had a mean repigmentation rate of only 77% [91].

Topical 2 % tofacitinib along with NBUVB was tried in 11 patients with vitiligo on the face for 2 to 4 months with a mean reduction of 70% in the VASI score [92].

Oral tofacitinib is primarily metabolised in CYP3A4 in the liver with minor contribution from CYP2C19. CYP3A4 inhibitors (ketoconazole) or strong CYP2C19 inhibitors (fluconazole) can affect the pharmacokinetics of tofacitinib thereby reducing the metabolism leading to increased tofacitinib levels. Such cases requires dose reduction to avoid dose dependant side effects [93].

In most patients oral tofacitinib is well tolerated, with upper respiratory tract infections and diarrhea being the most common adverse reactions observed by the patients other than arthralgia, weight gain, mild elevation of lipids and liver enzymes and dose‑dependent decrease in blood counts.[91] Rarely it can lead to malignancies like Non melanoma skin cancer (NMSC), solid organ tumors, melanoma and lymphoproliferative disorders.

7.2.2 Ruxolitinib

In a recent case report, the patient with concurrent vitiligo and alopecia areata was put on oral ruxolitinib 20mg twice daily for 20 weeks. The treatment was unsatisfactory as only facial lesions showed temporary improvement and then recurred at 12 weeks post treatment [94].

But topical ruxolitinib 1.5% cream with twice-daily application has fared well in a 20-week, open-label, pilot study conducted on 11 patients of vitiligo with maximum of 10% body surface area (BSA) involvement. Amongst the patients who completed the study mean improvement of 27% was recorded and maximum response was seen in facial vitiligo (mean reduction of 76% in VASI score) [95]. In an open label trial, 8 patients with vitiligo were treated with 1.5% topical ruxolitinib cream with optional NBUVB for 32 weeks which was completed by 5 people. Mean improvement of 92% was observed in vitiligo of the face and moderate response was observed in truncal lesions and response was sustained at 6 months follow up [96].

Mild erythema, transient acneiform eruptions and worsening of acne are commonly reported side effects with topical ruxolitinib treatment [95,96].

Best results are seen in patients with vitiligo on the face and upper extremities. Concurrent NBUVB and adequate sun exposure yielded excellent repigmentation as low dose light therapy is necessary to activate the melanocytes. [94-96]

7.3 STAT inhibitors

Response to oral simvastatin was first observed in a 55-year-old male being treated for uncontrolled hypertension with concurrent long-standing vitiligo [97].

Although the results were good in mouse model studies, average worsening of disease was observed in a double-blind, placebo-controlled, phase-II clinical trial with oral simvastatin. There was a mean increase of 26% in the VASI score in the treatment group compared to 0% change in the placebo group. Dosing limitations in humans owing to the potential toxicity of high dose simvastatin may be the cause of disparity in results compared to mouse model studies.

The side effects include occasional myalgia, diarrhoea, and mild elevation of creatine phosphokinase. Headache and vertigo can be troublesome enough to withdraw treatment [98].

To overcome the potential toxicities of high dose systemic statins, trials with topical atorvastatin with NBUVB [99] and topical Atorvastatin and simvastatin [100] are being conducted in vitiligo.

7.4 Alpha-Melanocyte-stimulating hormone (α-MSH) analogues

Afamelanotide [Nle4-D-Phe7]-α-MSH is a potent synthetic analogue of naturally occurring hormone alpha-melanocyte-stimulating hormone (α-MSH), with a greater affinity to the melanocortin 1 receptor (MC1R) and a longer half-life that can stimulate melanogenesis and facilitate transfer of eumelanin within the melanosome. It may also restore balance in cytokine environment by acting on inflammatory cells expressing MC1R (neutrophils and lymphocytes). In a randomized comparative multicenter trial, 28 patients were randomised to combination therapy (Afamelanotide plus NB-UV-B) and 27 into monotherapy with NBUVB to test the safety and efficacy of afamelanotide subcutaneous implants in generalised vitiligo. After receiving NB-UV-B for 1 month, 16 mg of afamelanotide subcutaneous implants were administered monthly to the combination therapy group while the other group received NB-UV-B monotherapy. Afamelanotide combination therapy was found to be superior (48.64% repigmentation) to NB-UV-B monotherapy (33.26% repigmentation) ($P < .05$). Earlier and better results were observed in face and upper extremities compared to trunk and lower extremities and no response was seen in the feet. Nausea, erythema and generalised skin hyperpigmentation were well-tolerated, although some subjects withdrew from the trial as the hyperpigmentation was socially unacceptable. [101]

7.5 Phototherapy

7.5.1 Bioskin

In an open label study of 458 patients with vitiligo to evaluate the safety and efficacy of Bioskin, a targeted 311-nm narrow-band-microphototherapy device, 370 patients were treated with bioskin either alone or in combination with other treatment modalities like betamethasone dipropionate 0.05% cream twice daily (28 patients), tacrolimus 0.1% ointment twice daily (59 patients), pimecrolimus 1% cream twice daily (63 patients), calcipotriol ointment 50μg/g twice daily (60 patients), and 10% L-phenylalanine cream twice daily (60 patients). Bioskin monotherapy had excellent repigmentation rates (> 75%) in 72% of patients and greater repigmentation was

achieved when combined with other treatment options. Maximum response was seen in combination with betamethasone dipropionate with 90.2% of patients showing > 75% repigmentation. This is devoid of generalised pigmentation and early photo-aging associated with whole body phototherapy but it would be inconvenient to irradiate large surface areas with targeted device and thus is suitable for lesions involving < 10% of BSA [102].

7.5.2 UV-A1 lasers

UV-A1 is a new powerful tool in the phototherapeutic armamentarium owing to its deeper penetration and immunomodulatory properties. In a preliminary study of 17 patients, 53% of the patients showed good to excellence response at the end of 8 weeks and the results were sustained at 12 weeks [103].

In a multicenter observational study to evaluate the safety and efficacy of Laser Alba 355, (A UV-A laser with 355nm spectrum) in the treatment of vitiligo vulgaris, 21 patients who had previously been treated unsuccessfully with other conventional phototherapies were recruited and were irradiated once a week at a dose of 120 J/cm² for 24 weeks. It was observed that 17 patients (81%) achieved excellent repigmentation (> 75% repigmentation) and 3 patients (14%) showed marked improvement with 50-75% repigmentation. Only one patient showed unsatisfactory response to the treatment. Side effects included mild erythema, itching and burning sensation and was well tolerated [104].

UVA - 1 laser mainly mediates the formation of reactive oxygen species, during the oxidative phosphorylation in the mitochondria and results in subsequent damage of DNA, proteins, lipids and cellular organelles. This may exert inhibition of immune responses and stimulate melanogenesis [104].

In another innovative study, a unique combination of Fraxel Herbium laser (Valseriana® Fraxel Herbium Laser), topical latanoprost and UV-A1 laser was used in 27 patients with vitiligo. All patients were first irradiated with single passage of Fraxel Herbium laser (wavelength of 1540 nm) at 1800 mJ/P followed by topical latanoprost 0.005% (Xalatan®) application (1 drops every 2.5*2.5 cm2 lesion). The day after, the lesions were irradiated with UVA1 laser for 20 minutes (Laser Alba 355®, the wavelength of 355 nm). The treatment was repeated every 21 days, for 9 months. Excellent repigmentation (> 75% repigmentation) was achieved in 27

patients (90%) with a mean value of 88% and 3 patients (10%) achieved marked repigmentation (50-75%). Adverse effects were limited to transient inflammation and erythema [105].

7.5.3 Photodymanic therapy

In a preliminary analysis of photodynamic therapy with 5-aminolevulinic acid (ALA) in treating vitiligo, 3 patients were treated with ALA at a drug concentration of 1.5%, applied for 3 hours before irradiation with UV-A at 80mw/cm2 for 20 min and was effective in treating vitiligo. The treatment was associated with mild pain and burning sensation, but no other adverse reaction was noted [106].

7.5.4 311nm Titanium:Sapphire laser

In an open-label trial, 14 patients with nonsegmental vitiligo of the face and neck were treated gain-switched 311-nm TSL (Pallas; Laseroptek) twice a week along with topical tacrolimus ointment 0.1% for 1.8-6.2 months. The median number of treatment sessions ranged from 13-47 and median cumulative dose ranged from 4400-24450 mJ/cm^2. 79% of the patients showed excellent to complete repigmentation after a median of 21 treatments and 3.7 months. 36% of the patients experienced persistent erythema for 48 hours, which improved spontaneously in 3 to 4 days [107] (Table 1). In another randomised non inferiority split body trial, 308nm excimer laser (EL) was compared with TSL in 21 patients having symmetrical vitiligo lesions. The results were comparable and TSL was as effective as EL in inducing remission with a good safety profile.[108]

7.6 Oral antioxidants

In a double-blind placebo-controlled trial, oral ginkgo biloba as a monotherapy significantly decreased progression of vitiligo compared to placebo [109] and in another double-blind placebo-controlled trial, NB-UVB along mixture of alpha lipoic acid, vitamin E, vitamin C and polyunsaturated fatty acids showed significant repigmentation rates and promoted dose reduction of NB-UVB[110]. When combined

with narrow band UVB, oral polypodium leucotomos has shown significant improvement in the repigmentation rates of head and neck lesions [111].

7.7 Topical immunosupressants

In a recent case report, a 23-year-old female with localised vitiligo was treated with topical methotrexate 1% gel twice daily for 12 weeks after unsuccessful treatment with many other treatment modalities. Significant repigmentation with no local or systemic adverse effects were observed at the end of the treatment. Methotrexate possibly alters expression of IL-6 and reactive oxygen metabolite production. It is also known to suppress TNF-α-mediated activation of nuclear factor-κB and subsequent anti-inflammatory and immunomodulatory properties [112].

In another open label study, 30 patients with localised vitiligo were treated with topical mycophenolate mofetil 15% twice daily for 3 months and repigmentation was assessed every month using the VASI score. At 3 months, the drug showed only minimal efficacy with only 36.6 % (n=11) of the patients showing 25% repigmentation. Although the drug is safe with no side effects, the efficacy is not up to the mark [113].

These topical immunosupressants can be used as steroid sparing agents in selected cases.

7.8 Basic fibroblast growth factor

In vitro studies have shown b-FGF to be mitogenic to melanocytes and activate melanogenesis and migration of perilesional melanocytes in the depigmented macules.

A multicentre phase IV double blind randomized control trial on bFGF related deca peptide was conducted with the objectives to evaluate the safety and efficacy of topical deca peptide in vehicle and in combination with NBUVB and to see if it was effective in repigmenting stable non segmental vitiligo macules on sun protected areas. Thirty-two patients were treated with deca peptide in vehicle and other 30

were treated with NBUVB either with or without topical application of deca peptide for 3 months. At the end period, nine out of 30 lesions achieved 40% repigmentation in NB-UVB plus decapeptide in vehicle group compared to only five of 62 lesions treated with NBUVB or peptide in vehicle monotherapy.

Basic fibroblast growth factor related deca peptide act synergistically with NB-UVB to produce pigmentation in the depigmented macules and was superior to NBUVB alone. It was observed that deca peptide alone, in the absence of exposure to sun may not be as effective in repigmenting vitiligo. It was well tolerated in the patients [114].

In another comparative study, bFGF related deca peptide was observed to be superior to Betamethasone Valerate 0.1% Ointment in treating vitiligo [115].

7.9 Targeted Immunotherapy

Many studies underlined the role of cytokine and signalling molecule imbalance in the pathogenesis of vitiligo and its association with elevated cytokines like TNF - α, INF - γ, IL -1, IL - 2, IL - 6, IL - 8, IL - 17.With the increasing knowledge about the pathogenesis of vitligo, newer molecules targeting the specific immune pathway are being developed as the need of the hour to combat the problem of lack of safe and efficacious drugs in treating vitiligo.

Keeping in mind the efficacy of rituximab (a murine/human monoclonal antibody to CD20) in autoimmune diseases, pilot study was undertaken in which five patients with active vitiligo were given 1 g of rituximab in a single intravenous infusion and followed-up for 6 months. Excellent clinical and histological improvement was noted in three patients and one patient presented with slight improvement. No improvement was seen in one patient. Authors are of the opinion that these results prompt for further clinical trials of human monoclonal antibody to CD20 in treating vitiligo [116].

Neovir® an intramuscular immunomodulatory agent, composed of sodium oxo – dihydro – acridinyl - acetate (ODHAA) normally used in multiple sclerosis, immunodeficiencies and oncological diseases. An experimental study 60 patients with active non-segmental vitiligo were treated with ten doses of ODHAA every 48

hours and progression of vitiligo was monitored at 1, 3, 6 and 12 months after treatment. The results were excellent and high efficiency observed in achieving long-term stabilisation of nonsegmental vitiligo [117].

Recently, researchers have explored the role of low dose cytokines, growth factors and neuropeptides in treating vitiligo. In details, oral consumption of 20 drops of low dose anti-inflammatory cytokines (IL - 4 and IL -10 ; low dose anti-IL1 antibody and b - FGF) twice a day, for 9 months, was helpful in restoring the altered interaction between keratinocytes and melanocytes, leading to skin repigmentation [118].The combination of more conventional treatments with low dose cytokines (e.g. topical corticosteroids or phototherapy) may provide better results in terms of repigmentation rate.

Abatacept, a fusion protein is linked to extracellular domain of CTLA-4, an immune checkpoint regulator, by Fc region of the immunoglobulin IgG1 and currently FDA approved for the treatment of rheumatoid arthritis. An open label, pilot study was started to test the efficacy of Abatacept in treating vitiligo [119].

7.10 Future therapeutic prospects

PD-1 ligand (PD-L1, a PD-1 agonist) is currently under preclinical trials for treating psoriasis and inflammatory bowel disease [120]. Considering its role in maintaining immune balance this could be a therapeutic option in future.

IL15 acts via JAK STAT signalling pathways and has been recently implicated in oxidative stress mediated destruction of melanocyte. Researchers are of the opinion that targeting IL15 – JAK STAT interactions could be an option to be explored in future [81].

In an attempt to study the effect of miR-155 on the proliferation of CD8+ T cells, Treg cells and melanocytes, a recent report demonstrated capability miR-155 agonist in significantly increasing the Treg cells expression, thereby reducing the rate of CD8+ T cell expansion, as well as promoting melanocyte proliferation. Therefore, induction of mi-RNA may possibly be a future prospect for the treatment of vitiligo.

A wide array of HLA associated genes including HLA-A2, A30, A31, B13, B27, B46, B56, B60, Cw4, Cw6, DR4, DR5, DR7, DR53 and DQ3 have been implicated in the causation of vitiligo in different populations. Other genes on the MHC region like Low molecular weight polypeptide-2 and -7 (LMP2 and LMP7) and transporter associated with antigen processing protein-1 (TAP-1) have also been associated with generalized vitiligo. Thus, this foci may be considered a novel target for gene therapy in different populations.

Mutations in or near CAT gene encoding for catalase enzyme may be responsible for quantitative deficiency of catalase in vitiligo patients. Other functional candidate genes associated with vitiligo are Platelet-derived growth factor receptor alpha (PDGFRA) gene, Protein tyrosine phosphatase non receptor 22 (PTPN22) gene, Melanocyte proliferating gene 1(MYG1), Microphthalmia- associated transcription factor (MITF) gene, Cluster of differentiation 117 (CD117) gene, Estrogen receptor (ESR) 1 gene Estrogen receptor (ESR) 1 gene, Endothelin-1 (EDN1) gene, Cyclooxygenase-2 (COX2) gene. These genes may be good therapeutic targets in the future.[121]

7.11 Competitive environment

With the ongoing developments in understanding, the pathogenesis of vitiligo and use of specific molecular targets in treating vitiligo the market size is expected to reach $2B by 2026. However, the currently available of moderately effective, cheap off-label medications – like Tacrolimus / Pimecrolimus,topical corticosteroids, etc. may hinder growth of the vitiligo drugs market.

The top key players in are Incyte (topical Ruxolitinib) and Pfizer (PF-06651600 as JAK3 inhibitor), both with active clinical trials underway. Other companies with mainly off-label vitiligo products include Astellas Pharma (Protopic), Bausch Health (Methoxsalen), Bristol-Myers Squibb (Abatacept), Celgene (Apremilast), Dr. Reddy's Laboratories (Melgain), Puneet Laboratories (Albaquin), Sesderma (Vitises).

Ache Laboratorios Farmaceuticos had reportedly has set aside $100M for development of vitiligo candidate drug ACH24 and was expected to complete phase III trials in 2013 but recruitment was withdrawn due to reasons not specified.[122]

Aclaris therapeutics lead phase II clinical trial in JAK 1/3 inhibitor ATI-50002 topical solution twice-daily in adults with non-segmental facial vitiligo involving atleast 0.25% of body surface area, which was expected to be completed by September 2019.[123] Dermavant Sciences has announced Phase IIa randomized, double-blind, vehicle-controlled study to assess the safety, tolerability, and systemic exposure of cerdulatinib gel, 0.37% in adults with vitiligo with plans of releasing prelimnary results in earl 2020. This is a combined janus kinase and spleen tyrosine kinase inhibitor.[124] (Table 2)

8 Potential development issues

The wide array of molecules targeting a specific immune response are currently in development by various pharmaceutical companies. One main issue that may arise during the development would be the diversity and complexity of pathomechanisms involved, that a single molecule cannot be zeroed in for effective treatment. Although many cytokines like TNF - α, INF - γ, IL -1, IL - 2, IL - 6, IL - 8, IL – 17 have been found to be elevated in vitiligo, inhibitors of not all of these have been successful in treating the same. TNF-alpha inhibitors expected to interfere with repigmentation by dose-dependent inhibition of melanocyte proliferation and tyrosinase activity and also by promoting melanocyte apoptosis [125]. Although few studies have shown the efficacy of TNF-alpha inhibitors in halting the disease progression, no satisfactory repigmentation was achieved [126,127] and also there were numerous paradoxical reports of de-novo vitiligo after the use of TNF-alpha inhibitors for other indications [128].

Similarly, IL 17 and Th17 pathway was implicated in the pathogenesis of vitiligo in many studies but use of IL 17 inhibitors did not yield good results in pilot studies. Speackart et al. concluded that the increased IL-17 levels in vitiligo was most likely due to increased percentages of Th17.1 lymphocytes, which is an intermediate phenotype between Th1 and Th17 cells and IL17 inhibition possibly has no role in treating active vitiligo [129].

These scenarios necessitate the need for finding novel clinical markers in vitiligo that can help select the mode of treatment and also serve as an indicator of treatment

success. Recent studies have shown CXCR3 and CCL10 as markers of active non-segmental vitiligo and these markers can be used to assess the efficacy of JAK inhibitors in treating vitiligo. More markers need to be defined to help choosing the correct line of treatment and accurate assessment of treatment success at the molecular level, much before the onset of clinical improvement.

The second issue would be lack of uniform consensus on disease severity and outcome assessment in different clinical studies and trials. There is a need for definitive assessment protocol and defining the objective limit of satisfactory treatment as per both physicians and patient's needs.

Keeping the current goals in mind, there also needs to be more trials with combination therapies to address the different aspects of treatment including halting the disease progress, activation of melanogenesis and sustained response during the follow up, as the main challenge faced by the researchers is prevention of recurrence.

9 Conclusion

To conclude, vitiligo is a multifactorial disease with a complex etiopathogenetic mechanisms but lacks a definitive understanding of the same resulting in lack of definitive safe and efficacious treatment. The long-standing course and the burden of long duration of treatment with modest efficacy has drained the patients of emotional stability and comfort adding the large cohort of psychologically deprived individuals. The currently available modes of treatment need to be replaced with newer definitive treatment modalities. JAK-STAT inhibitors have been promising in this aspect by achieving upto 92% repigmentation in sunexposed sites, but cost can be limiting factor. This along with the newer laser and phototherapy modalities can achieve good results. Surgical modalities are still a favourite in treating long standing stable vitiligo and are also cost effective.

10 Expert opinion

The treatment of patients with vitiligo cannot be approached with a unified module, rather has to be tailored as per individual requirements, also keeping in mind patient's expectation of the treatment outcome, affordability and the likelihood of compliance. The patients can be categorised to segmental and nonsegmental vitiligo with either stable or progressive disease.

Those with active progressive disease will need an aggressive approach to halt the progression and can be treated with NB-UVB if the disease is generalised. Basic fibroblast growth factor in combination with NB-UVB is an effective mode in localised vitiligo. Combining NB-UVB with various other drugs like topical calcineurin inhibitors, topical calcipotriol, antioxidants and topical immunomodulators have shown synergistic activity in many studies and can be used. Off late UV-A1 lasers have entered the main stream therapeutics along with NBUVB and are very effective in inducing repigmentation in vitiligo in generalised type. In places where this is available, it can be started as the 1st line of treatment in selected cases.

JAK inhibitors have been promising in the treatment of vitiligo in the recent years, owing to its specificity in targeting the IFN – γ mediated melanocyte damage and proven to be safe when applied topically. This, with a repigmentation rates up to 92% in facial areas and sun exposed areas can be now considered a front line option in localised vitiligo limited to <10 % body surface area along with adjuvant NB-UVB which assist in melanocyte activation and melanogenesis.

In case of unavailability or unaffordability, potent topical steroids once daily can be used in both adults and children in non-facial vitiligo and still classify as effective drugs, albeit the risk of topical side effects. On the face and sensitive areas in young children, topical calcineurin inhibitors and calcipotriol can safely be used.

Off late topical immmunosupressants like methotrexate gel 1% and topical mycophenolate mofetil have shown good efficacy in halting disease progression and well tolerated with only few minor side effects like erythema and burning which spontaneously resolves. Further studies supporting the use of these medications may prove to be helpful in avoiding the menace caused by unregulated steroid use in patients.

In patients not responding to topical medications, low dose oral corticosteroids given as a pulse therapy on two consecutive days in a week may be used to halt disease

progression and can be supplemented with oral antioxidants to manage the oxidative stress in vitiligo. This, supplemented with NB-UVB may be more efficacious than the monotherapy. Long term treatment with oral corticosteroids are associated with the risk of side effects like weight gain, hypertension, diabetes mellitus, osteoporosis and suppression of HPA axis.

These side effects can be overcome by use of steroid sparing agents like oral azathioprine, cyclosporine and methotrexate. Few comparative studies have shown similar efficacy compared to OMP in this group of drugs. Nevertheless, this needs to be substantiated with larger randomised studies for better understanding of their efficacy. These are mostly well tolerated in low doses, but can still be associated with mild dose dependant side effects which can be easily monitored by routine blood investigations.

Minocycline, a potent immunomodulator and antioxidant has shown efficacy comparable to dexamethasone mini pulse and can be tried in patients with active progressive vitiligo. Other oral antioxidants like Gingko Biloba, polypodium leucotomos, lipoic acid, vitamin E etc. are effective in combating the oxidative stress and can be added as an adjuvant to the immunosuppressive treatment to get better results.

Oral tofacitinib has demonstrated good results in patients with facial vitiligo and when used with adjuvant phototherapy. However, its use is limited by the occurrence of side effects like activation of latent infections, elevation of lipid levels, liver functions and also the cost.

Most cases on the face, trunk and extremities repigment with the above-mentioned modalities but the lesions on the bony prominences, acral areas and mucosa have proven to be resistant time and again. Bony prominences may be successfully treated with monochrome excimer laser as observed in the studies.

In those cases stabilised by any of the treatment modalities, with no repigmentation, surgical treatment by either blister roof grafting or epidermal melanocyte keratinocyte transfer or follicular melanocyte transfer can be beneficial. Surgical treatment in combination with NB-UVB yields better results than surgery alone.

Afamelanotide, a synthetic analogue of α-MSH injected subcutaneously is a new promising drug in inducing repigmentation of the depigmented patches in a stable vitiligo patient.

All these modalities apart, the future of vitiligo treatment relies on the development of more specific drugs like the CTLA4 modulators, PD1 ligands and anti IL15 molecules etc.

Stem cell regenerative modalities may be yet another promising treatment aspect in the future.

To conclude treatment of vitiligo needs multimodal approach with three different aspects being targeted at the same time. First being, minimising the oxidative stress and optimising the melanocyte micro environment, second being the immunomodulatory and immunosuppressant action and last being the regeneration of melanocytes. Various modes achieving each of these targets combined together gives the best results in treating vitiligo.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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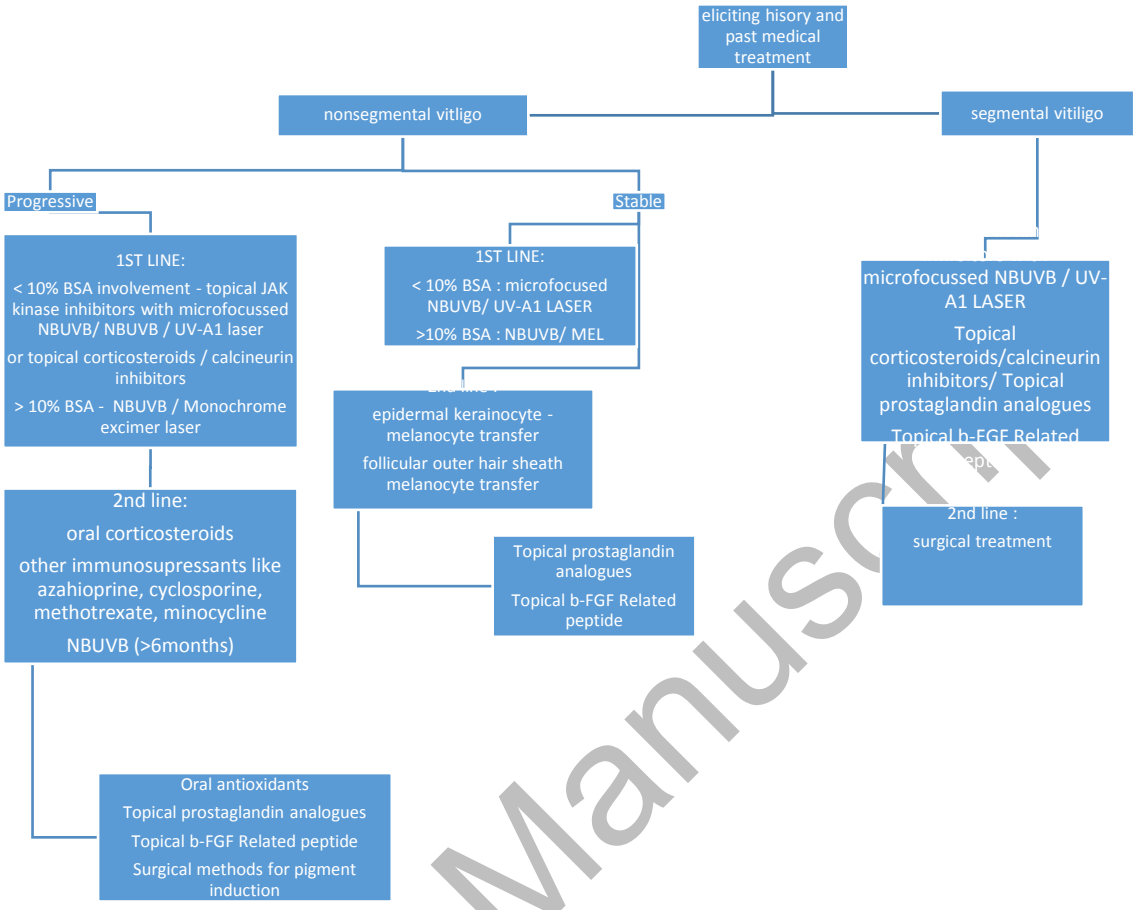

Figure 1. Treatment based on type of vitiligo

Table 1. New treatment strategies for vitiligo

AUTHORS	TYPE OF REPORT/	NO OF PATIENTS	FORMULATION AND DOSAGE / ADJUVANT TREATMENT	DURATION	TYPE/ SITE OF VITILIGO	RESULTS
SYTEMIC IMMUNOMODULATORS						
Singh A et al [81]	Randomized controlled Study	50	Minocycline 100 mg/day (Group I - 25 patients) vs 2.5 mg dexamethasone on 2 consecutive days in a week (Group II - 25 patients)	6 months	active progressive vitiligo	Both groups had similar repigmentation rates and reduction in VASI and VIDA.
Singh H et al [82]	Randomized comparative study	52	Group 1 : 10 mg methotrexate weekly VS Group 2: dexamethasone 2.5 mg, taken on 2 consecutive days in a week.	6 months	active vitiligo	Patients in both groups had a similar reduction in the vitiligo disease activity score at the end of the study
Taneja et al [83]	Open label study	18	3mg/kg/day oral cyclosporine	3 months	active vitiligo	11 out of 18 (61%) patients had halting of disease progression.. 9 also showed repigmentation. The mean VASI score improved by 0.43 (P = 0.0016) from 4.56 to 4.13
Jak kinase inhibitors						
Tofacitinib						
Craiglow et al [81]	Case report	1 50 y, F	Tofacitinib PO 5mg alternate days × 3 week, and then 5mg daily	5 months	Acral, facial and trunk	Complete pigmentation of forehead, depigmented area reduced from 10% to 5 % BSA

Gianfaldoni et al [83]	Open label Randomised Study	A)58 Vs B) 9	A)Micro focussed NBUVB once in a weeks × 12 sessions vs B) Tofacitinib 10 mg PO daily + Micro focussed NBUVB	3 months	A) GV (Vitiligo) vs B) (vitiligo, Rheumatoid Arthritis)	group A had good results with a mean of 77% repigmentation in 42 patients. All the patients in group B had near complete repigmentation with a mean 92% repigmentation.
Liu et al [82]	Case series	10	Tofacitinib 5-10 mg PO BID NB-UVB in 2 patients	9.9 months	8 GV, 2 acral	sun exposed areas in 3 patients has best response, whereas minimal or no response in sunprotected areas. complete repigmentation in 1 patient with NBUVB.
McKesey et al [84]	Open Label Pilot trail	11	2% tofacitinib cream BID + (NB-UVB) thrice weekly	2-4 months.	facial	Good to excellent repigmentation .A mean improvement of 70% noted.
Ruxolitinib						
Rothstein, et al[87]	Open Label proof-of-concept trial	12	Topical ruxolitinib 1.5% cream BID daily	20 weeks	NSV	facial vitiligo showed mean VASI improvement of 76% . Acral areas responded poorly.
Joshipura et al [88]	Open label	8	Topical ruxolitinib 1.5% cream BID + Optional NB-UVB	32 weeks	not reported	92% improvement in mean VASI score in facial areas and 12.6% in upper extremities.
Stat inhibitors						
Noel M et al [89]	Case report	1	Simvastatin 80 mg PO daily	6 months	Facial and acral	Moderate repigmentation noted

Vanderweil SG [90]	Double blinded-randomised control trial	15	Simvastatin 40 mg PO daily for 1 month ,then 80 mg daily for 5 months	6 months	Nonsegmental	Mean increase of 26% in the VASI score in study group compared to placebo group .
Alpha-Melanocyte-stimulating hormone (α-MSH) analogues AFAMELANOTIDE						
Lim et al [93]	Randomized comparative multicenter trial	55	Afamelanotide plus NB-UV-B (280 vs NB-UVB alone(27)	5 months	Nonsegmental	. Afamelanotide combination therapy (48.64% repigmentation) was found to be superior to NB-UV-B monotherapy (33.26% repigmentation) (P < .05). Earlier and better results were observed in face and upper extremeties
Phototherapy						
Lotti et al [94]	Open label study	458	311-nm narrow-band-microphototherapy (BIOSKIN) every 2 weeks	6 months	nonsegmental	excellent repigmentation rates (> 75%) in 72% of patients with bioskin alone and Maximum response 90.2% of patients with combination of betamethasone dipropionate with bioskin
Lotti et al [95]	Multicenter observational study	21	UV-A1 Laser once a week at a dose of 120 J/cm²	24 weeks	nonsegmental	17 patients (81%) achieved excellent re - pigmentation (> 75% repigmentation) and 3 patients (14%) showed marked improvement with 50-75% repigmentation
Lotti et al [96]	Open study	27	single passage of Fraxel Herbium laser at 1800 mJ/P followed by topical latanoprost 0.005% (Xalatan®) and	repeated every 21 days, for 9 months.	nonsegmental	Excellent re - pigmentation (> 75% repigmentation) was achieved in 27 (90%) mean value of 88% and 3 patients (10%) achieved a marked

			irradiated with UVA1 laser for 20 minutes a day after that.			repigmentation (50-75%
zhang et al [97]	Case series	3	Amino Levulinic Acid at a drug concentration of 1.5% applied for 3 hours, before irradiation with UV-A at 80mw/cm2 for 20 min	3 months	nonsegmental	effective in treating vitiligo but requires futher studies
Bae et al [98]	Open-label trial	14	gain-switched 311-nm Titanium Sapphire Laser(Pallas; Laseroptek) twice a week along with topical tacrolimus ointment 0.1%	1.8-6.2 months.	nonsegmental vitiligo of the face and neck	79% of the patients showed excellent to complete repigmentation after medians of 21 treatments and 3.7 months.
Oral antioxidants						
parsad et al [99]	Double-blind placebo-controlled trial	47	Gingko biloba extract 40 mg three times daily	6 months	nonsegmental	statistically significant cessation of progression of disease noted(P = 0.006).
Dell anna et al [100]	Randomized, double-blind, placebo-controlled multicentre trial.	35	The treatment group received combination of alpha-lipoic acid, vitamins C and E, and polyunsaturated fatty acids for 2 months before and for 6 months during the NB-UVB treatment	8 months	nonsegmental	increased efficacy of NB-UVB, with 47% of the patients achieving > 75% repigmentation vs. 18% in the placebo group (P < 0.05)
Middelkamp‐Hup MA et al	Randomized double-	50	250 mg oral polypodium leucotomos or placebo	25-26 weeks.	vitiligo vulgaris	higher Repigmentation noted in the P. leucotomos group vs.

[101]	blind placebo-controlled study.		three times daily, combined with NB-UVB twice weekly			placebo in the head and neck area (44% vs. 27%, P = 0.06). Patients attending more than 80% of required NB-UVB sessions showed increased repigmentation in the head and neck area in the P. leucotomos group
Topical immunosupressants						
Abdelmaksoud A et al [102]	Case report	23/F	Methotrexate 1% gel twice daily	12 weeks	Focal vitiligo	significant repigmentation noted
Handjani F et al [103]	Open label study	30	Topical mycophenolate mofetil 15% twice daily	3 months	localised vitiligo	36.6 % (n=11) of the patients showed 25% repigmentation
Basic fibroblast growth factor						
Ramaiah et al [104]	Multicentre phase IV double blind randomized control trial	A)32 VS B)30	A) Deca peptide in vehicle VS B)NBUVB either with or without topical application of deca peptide	3 months.	nonsegmental vitiligo	, 9 of 30 lesions achieved 40% repigmentation in NB-UVB plus decapeptide in vehicle group compared to only 5 of 62 lesion treated with NBUVB alone and with peptide in vehicle.
Subhashini PK et al [105]	A prospective, comparative and Intervention al study	62	31 in group A on topical Basic fibroblast growth factor (b FGF) 0.1% solution and 31 in Group B on topical (BV) 0.1% ointment	16 weeks	nonsegmental vitiligo	45% (n=14) of the patients treated with bFGF, showed more than 75% repigmentation compared to 7% in betamethasone group showing 50 – 75% repigmentation
Rituximab						
Ruiz‐Argüelles A et al [106]	Case series	5	1 g Rituximab in a single intravenous infusion	followed-up for 6 months.	active disseminated vitiligo	Three of the patients showed an overt clinical and histological improvement of the disease, one presented slight

						improvement
Sodium oxo – dihydro – acridinyl - acetate (ODHAA)						
Korobko IV et al [107]	Experimental study	60	10 doses of ODHAA I.M every 48 hours	monitored at 1, 3, 6 and 12 months after treatment	active non - segmental vitiligo	The results were excellent and high efficiency observed in achieving long-term stabilisation of nonsegmental vitiligo

Table 2. Emerging drugs in phase II and phase III for vitiligo

Compound	Company		Stage of	Mechanism of

		Structure	Development	Action
ACH24	**Ache Laboratorios Farmaceuticos**		Phase III	
ATI-50002 ATI-1777	**Aclaris Therapeutics**	Small molecules	Phase II Preclinical studies	Janus kinase 1 inhibitors/Janus kinase 3 inhibitors
ARN-4079	**Arrien Pharmaceuticals**	Small molecules	Phase I	Emt protein-tyrosine kinase inhibitors; Janus kinase inhibitors
AX-1602	**AXIM Biotechnologies**	Cannabinoids	Phase I	Cannabinoid receptor modulators
BOS-475	**Boston Pharmaceuticals**	Small molecules	Phase I	Bromodomain and extraterminal domain protein inhibitors
DMVT-502	**Dermavant Sciences**	Small molecules	Phase II	JAK/Syk inhibitor
HuABC2	**JN Biosciences**	NA	NA	Suppress CD122/CD132-bearing NK and memory T cells
MC-1	**Palatin Technologies**	Small molecules		Melanocortin receptor agonists: type 1, type 2,

				type 3, type 4, type 5. Melanocortin type 5 receptor modulators
excimer laser	**Ra Medical Systems**	Phototherapy	NA	NA

NA:Not applicable