

REVIEW ARTICLE

Concise review of recent studies in vitiligo

Mohamed Allam¹, Hassan Riad²

Address for Correspondence:

Mohamed Allam

¹Dermatology Department, Hamad Medical Corporation, Doha, Qatar

²Dermatology Department, Rumailah Hospital, Hamad Medical Corporation, Doha, Qatar
Email: mallam@hmc.org.qa

<http://dx.doi.org/10.5339/qmj.2013.10>

Submitted: 6 November 2012

Accepted: 20 October 2013

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Cite this article as: Allam M, Riad H. Concise review of recent studies in vitiligo, Qatar Medical Journal 2013;10 <http://dx.doi.org/10.5339/qmj.2013.10>

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ABSTRACT

Vitiligo is an acquired pigmentary disorder of the skin and mucous membranes which manifests as white macules and patches due to selective loss of melanocytes. Etiological hypotheses of vitiligo include genetic, immunological, neurohormonal, cytotoxic, biochemical, oxidative stress and newer theories of melanocytorrhagy and decreased melanocytes survival. There are several types of vitiligo which are usually diagnosed clinically and by using a Wood's lamp; also vitiligo may be associated with autoimmune diseases, audiological and ophthalmological findings or it can be a part of polyendocrinopathy syndromes. Several interventions are available for the treatment for vitiligo to stop disease progression and/or to attain repigmentation or even depigmentation. In this article, we will present an overall view of current standing of vitiligo research work especially in the etiological factors most notably the genetic components, also, types and associations and various and newer treatment modalities.

BACKGROUND

Vitiligo is the most common depigmentation disorder where the selective destruction of functioning melanocytes causes depigmentation of the skin, hair and mucosal surfaces.^(1,2) It affects approximately 0.5% to 1% of the population, with an average age of onset at about 24 years, its prevalence appears to be equal between men and women^(3,4) and there is no difference in the rate of occurrence according to skin type or race.⁽⁵⁾ Several etiological factors have been suggested,^(6,7) for which the most compelling evidence involves a combination of environmental, genetic and immunological factors interacting to contribute to autoimmune melanocyte destruction.⁽⁸⁾ Vitiligo is classified according to Picardo and Taieb⁽¹⁾ into four types: Non-segmental vitiligo (NSV), segmental vitiligo (SV), mixed NSV and SV, and unclassifiable types e.g., focal, multifocal

asymmetrical non-segmental and mucosal at one site. NSV is divided into subtypes: focal at onset, mucosal, acrofacial, generalized and universal.⁽¹⁾ Generalized vitiligo may begin later in life, at sites sensitive to pressure, friction, and/or trauma, and is typically progressive with flare-ups. Hair is affected at later stages. There is often an associated personal or family history of autoimmune disorders (AI).⁽⁹⁾ SV typically begins in childhood,^(10,9) most commonly in the face, with polices, and tends to be stable.^(11,10) Treatment of vitiligo aims at minimizing or preventing the disease progression, attaining repigmentation or depigmentation and achieving satisfactory cosmetic pleasing results. There are numerous medical and surgical interventions available to treat vitiligo, but understanding the available options, setting the appropriate treatment plans and tailoring it to our patients is extremely important.

ETIOLOGIC FACTORS

Vitiligo is a common skin disorder characterized by depigmented white patches in the skin due to loss of melanocytes. It remains unclear what causes damage or death to the melanocytes, there are many potential pathophysiological theories involving autoimmune, neural, autocytotoxic, biochemical, oxidative stress, melanocytorrhagy, and decreased melanocyte survival hypotheses. All of these proposed hypotheses or the pathological mechanisms result in the development of vitiligo. Autoimmune theory is more prominent in generalized vitiligo, which is considered a complex disorder involving combined pathogenic effects of multiple susceptibility genes and unknown environmental factors⁽¹²⁾ that lead to autoimmune destruction of melanocytes.⁽⁸⁾ Moreover, patients with genetic variants (GV) and their close relatives have elevated frequencies of certain other autoimmune diseases,^(12,13) suggesting that they have inherited specific diathesis of autoimmune diseases mediated by shared susceptibility genes or in other terms GV is a part of broader genetically mediated autoimmune diathesis.⁽⁸⁾

Neural theory is likely to underlie more localized types like segmental and focal vitiligo⁽¹⁴⁾ while melanocytorrhagy may explain the lesions caused by Koebner phenomenon.⁽¹⁵⁾

The current thought is that vitiligo represents a group of heterogeneous pathophysiologic disorders with a similar phenotype.⁽⁵⁾ The convergence theory states that stress, accumulations of toxic compounds, infection, autoimmunity, mutations, altered cellular

environment, and impaired melanocyte migration can all contribute to the pathogenesis.⁽¹⁶⁾

GENETICS

Researchers from different areas of the world explored intensively the possible shared susceptibility genes involved in vitiligo and other autoimmune diseases and additional genes that may mediate the vitiligo itself. Four different approaches have been used to identify genes that mediate the susceptibility to vitiligo: gene expression analyses, candidate gene association studies, genome-wide linkage studies and genome wide association studies (GWASs). Gene expression studies in vitiligo were done to analyze the changes in the expression pattern of several genes associated with immunomodulation, melanogenesis, and regulation of the development and survival of melanocytes.

In this context, IFN- γ , TNF- α and several members of interleukin-10 family cytokines (IL-10, IL-22, IL-24) and their receptors (IL10RA, IL10RB) have previously been demonstrated to be associated with vitiligo pathogenesis.^(17,18) There was a significant increase in the expression of IFN- γ , TNF- α and IL 10 in involved and adjacent uninvolved skin in vitiligo patients compared with healthy controls at baseline before the start of topical tacrolimus 0.1% ointment treatment, post treatment with tacrolimus 0.1% ointment twice daily for 24 weeks, there was a significant decrease in the expression of TNF- α 1. These data suggest that an imbalance in cytokines expression may have a role in the pathogenesis of vitiligo and decreased expression of TNF due to treatment with topical tacrolimus was associated with repigmentation.⁽¹⁷⁾

Reimann et al.,⁽¹⁹⁾ studied the mRNA expression profile of cytokines from IL-10 family and their receptor subunits (IL20RB, IL22RA2, IL26, IL-28A, IL-28B, IL29, IL28RA), MDM 1, IFNA1, IFNB1, IFNG, and ICAM 1 in the skin and peripheral blood mononuclear cells in vitiligo patients and controls and analyzed their potential connection to pathogenesis of vitiligo.

Melanocortin system in the skin responds to external and internal stresses through local pigmentation, immune, epidermal, adnexal, and vascular structure to stabilize skin function and prevent disruption of internal homeostasis.^(20,21) A reduction in the level of the proopiomelanocortin (POMC) peptide, α -MSH, has been demonstrated both in lesional skin and serum of vitiligo patients.^(22,23) Also, Graham

et al.,⁽²⁴⁾ demonstrated low expression of α -MSH in the lesional skin of vitiligo patients.

Kingo et al.,⁽²⁵⁾ studied the mRNA expression levels of eight genes from melanocortin system (POMC, ASIP, AGRP, MC1R, MC2R, MC3R, MC4R, MC5R) and two enzymes involved in melanogenesis (TRP1, DCT) from lesional and non-lesional skin of vitiligo patients and non-sun-exposed skin from healthy controls. They demonstrated decreased expression of these genes in the lesional skin, on the other hand, this study demonstrated significant increase in the expression in non-lesional skin from vitiligo patients compared to healthy subjects which was not described previously and they explained this increased expression by systemic compensation to restore normal pigmentation in lesions.

Over the past few years candidate gene association studies have been largely replaced by the GWASs to avoid or control the small sample size and thus insufficient power, failure to adequately correct for multiple testing, and population stratification artifacts, all of which greatly increased the risk of false positive associations. The most eminent work on GWAS of GV was done in Europe-derived white population^(26–28) and Chinese Han population.^(29,30) These studies identified a total of 17 proposed GV susceptibility loci, yielding a major insight into pathways of disease pathogenesis and overall strongly supporting an autoimmune basis of typical generalized.⁽³¹⁾

One study was carried out in the isolated mountainous region of Northern Romania where the community has grown in a continuous isolation since 1603, with essentially no historical immigration or emigration. In the most recent census (2004), the community had a population of 1673 individuals. The prevalence of GV is 2.9%. One single nucleotide polymorphism (SNP) achieved genome-wide significance for the gene *SMOC2* on chromosome 6 near *IDDM8*, which is a type 1 diabetes-rheumatoid arthritis locus.⁽²⁶⁾ Another study was also carried out in European-derived white population where 1514 patients compared with 2813 controls, where 579, 146 SNPs were genotyped and resulted in the identification of a total of 13 susceptibility loci for GV, including HLA class 1 (specifically HLA-A*0201), HLA class 11, *PTPN22*, *RERE*, *FOXP1*, *LPP*, *CCR6*, *IL2RA*, *TYR*, *GZMB*, *NLRP1*, *UBASH3A*, and *C1QTNF6*.^(27,28) Other GWASs were done on Chinese Han population with the identification of GV susceptibility loci in HLA class 1 and class 11 and likewise *CCR6*.^(29,30)

Virtually all of these reported susceptibility loci encode known immunoregulatory proteins, and many have been associated with genetic susceptibility to other autoimmune diseases that are epidemiologically linked to GV,⁽³¹⁾ with an exception among these susceptibility loci is *TYR* which encodes tyrosinase which is the key enzyme in melanin biosynthesis in melanocytes. In GV, *TYR* may act primarily to modulate recognition of the melanocyte target cells by the immune system and beyond its role in pigmentation tyrosinase is the major autoantigen in GV. Two *TYR* allele variants are known, *TYR* 402Arg and *TYR* 402Gln. For patient with GV, *TYR* 402Arg is considered the causal susceptibility variant and interestingly this *TYR* polymorphisms represents inverse relationship between vitiligo and malignant melanoma because patient with *TYR* 402Arg can effectively present tyrosinase which is major antigen on the surface of melanocytes and malignant melanoma cells in association with HLA-A*0201 so it can be recognized by the immune system and eventually can lead to immune destruction of melanocytes resulting in vitiligo and destruction of melanoma cells leading to regression of malignant melanoma so the development of GV in Malignant melanoma is considered auspicious prognostic sign. However, on the other hand the *TYR* 402Gln variant results in unstable polypeptide that is retained in the endoplasmic reticulum and degraded, thereby reducing the amount of tyrosinase presented on the cell surface thus imposing lower susceptibility to GV but greater risk of melanoma.^(31,27)

Also, one more study reanalyzed the genome-wide data set to test association of the 33 biological candidate genes previously implicated in GV to identify independent susceptibility loci For GV not shared by other autoimmune diseases, three susceptibility loci were identified *TSLP*, *XBP1* AND *FOXP3*.⁽³²⁾ Two more studies identify genetic associations of *NALP1* with GV.^(33,34)

HUMORAL AND CELLULAR IMMUNITY

It is clear that altered cellular immunity is present in vitiligo, in addition to and perhaps in combination with a humoral immune response.^(35,5)

Humoral immunity

There is a strong evidence that vitiligo is preferentially an autoimmune disease.⁽³⁶⁾ The association of with autoimmune conditions such as Addison's disease, hypothyroidism and pernicious anemia; as well as the presence of some alleles of MHC II antigens and other

autoimmune susceptibility genes; couple to the detection of organ-specific antibodies (ANA, anti-gastric parietal cells) in the sera of patients with vitiligo; together with the positive response to topical immunosuppressive therapy (topical steroids and tacrolimus); plus the studies in animal models of vitiligo and the participation of immune cells especially the demonstration of autoreactive T cells and the presence of the presence of antibodies against different antigens in melanocytes; all these several aspects support this hypothesis.^(35,37)

Different circulating antibodies directed against melanocytes have been detected in the sera of vitiligo patients, these antibodies seem to be related to the extent of the lesions, being present in more than 90% in patients with greater extent and in 50% in patients with lesser extent.⁽³⁸⁾

Ali et al.,⁽³⁹⁾ studied the serum immunoglobulin profile of vitiligo patients and found a significant decrease in IgG and IgA serum levels with no change in serum IgM compared to controls, and they proposed that IgG anti-melanocyte antibodies may play a role in vitiligo as they can induce melanocyte damage in vitro by a complement mediated mechanism and antibody-dependent cellular cytotoxicity.

IgG anti-melanocyte antibodies may play a role in stimulation and inappropriate expression of HLA-DR and induction of ICAM-1 on melanocytes, and also increase of IL-8 production, MHC II complex molecules expressed in melanocytes can present antigens to CD4⁺ cells and initiate an immune response and ICAM-1 with its role in the adhesion of immune cells can also play a role in immunological reactions and inflammation resulting in melanocytotoxicity.⁽⁴⁰⁾

Studies using different techniques have demonstrated that antibodies in vitiligo are commonly directed to antigens with a molecular weight of 35, 40–45, 68, 70, 75, 88, 90, 110, 150, 165 kDa, corresponding to non-pigment cell proteins, pigment cell surface proteins, cytoplasmic pigment cell proteins and melanoma cell proteins. The few specific autoantigens identified include tyrosinase; tyrosine-related protein (TRP) 1/75 gp and 2; the melanosomal matrix protein gp 100 (pmel 17) and Melan A/MART.^(41,42)

The role of cellular mediated immunity (cytotoxic T cells and regulatory T cells)

Cutaneous depigmentation in vitiligo involves cytotoxic activity of autoreactive T cells, one study evaluated the percentage of the regulatory T cells

(Treg) among skin infiltrating T cells by immunoenzymatic double staining of CD3 and FoxP3, revealing a drastic reduction in the numbers of Treg in non-lesional, perilesional and lesional vitiligo skin.⁽⁴³⁾ One interesting study analyses the early dynamic events in a patient with segmental vitiligo associated with halo nevi. In this study clinical, histopathological and T-cell phenotypic analyses were performed during the early onset of a segmental lesion in a patient with associated halo nevi. Histopathological analysis revealed a lymphocytic infiltrate, mainly composed of CD8⁺ T-cells and some CD4⁺ T-cells around the dermo-epidermal junction. Flow cytometry analysis of resident T-cells revealed a clear enrichment of pro-inflammatory IFN- γ producing CD8⁺ T-cells in lesional skin compared to non-lesional skin. Using human leukocyte antigen-peptide tetramers (MART-1, tyrosinase, gp100), increased numbers of T-cells recognizing melanocyte antigens were found in segmental vitiligo lesional skin as compared with the non-lesional skin and blood. The findings from this study indicate CD8⁺ melanocyte specific T-cell mediated immune response in segmental vitiligo with halo nevi as observed in GV. But, it remains to be elucidated whether these findings can also be extrapolated to segmental vitiligo without associated halo nevi.⁽⁴⁴⁾ The percentages of skin infiltrating CD8⁺ CTLs and Tregs were evaluated by immunohistochemistry and revealed dramatically increased numbers of both CD8⁺ CTLs and Tregs in the perilesional skin of GV patients. However, peripheral Tregs were impaired in their ability to suppress the proliferation and cytolytic capacity of autologous CD8⁺T cells, suggesting that a functional failure of Tregs and the hyper-activation of CD8⁺ CTLs may contribute to progressive GV. These data indicate that reduced numbers and impaired function of natural Tregs fail to control the widespread activation of CD8⁺ CTLs, which leads to the destruction of melanocytes and contributes to the elevated frequency of various associated autoimmune diseases.⁽⁴⁵⁾ However, Zhou et al.⁽⁴⁶⁾ evaluated circulating regulatory T (Treg) cells, including CD4⁺CD25⁺FoxP3⁺ Treg cells and invariant natural killer T (*i*NKT) cells, as well as naïve and memory CD4⁺ and CD8⁺T cells and their cytokine production, in a cohort of 43 progressive NSV patients with race-, gender-, and age-matched healthy controls and found that general immunophenotypes of CD4⁺ and CD8⁺T cells and the percentage of CD4⁺CD25⁺FoxP3⁺ Tregs were comparable between

NSV and healthy controls. The conflicting data from this study regarding the role of regulatory T (Treg) cells in the pathogenesis of NSV necessitate further studies to evaluate the role of these cells (either reduced number or defective function) in mediating uncontrolled self-reactivity and cytotoxicity especially at tissue level.

Double strike hypothesis

In 2010, Michelsen presented a consolidated set of theses which explain the pathomechanisms of vitiligo and melanoma-associated hypopigmentation.⁽⁴²⁾ The main thesis is the double strike hypothesis, i.e. vitiligo is caused by at least two different major pathomechanisms: an antibody-based pathomechanism and a T-cell-based pathomechanism. The antibody-based pathomechanism is dominant in diffuse vitiligo, while the T-cell-based pathomechanism is dominant in localized vitiligo.

AUTOCYTOTOXICITY HYPOTHESIS

Toxic metabolites from direct environmental or occupational exposure to certain chemicals, principally phenols and catechols or through accumulation of byproducts due to inhibition of enzymes involved in melanin pathway can damage melanocytes of genetically susceptible individuals. This hypothesis might be of importance in what is called chemical leukoderma or contact/occupational vitiligo.⁽⁴⁷⁾

OXIDATIVE STRESS HYPOTHESIS

Both lesional and non lesional skin of vitiligo has abnormal low level of catalase enzyme, which correlates with high H₂O₂ levels throughout the epidermis.^(48,49) A single nucleotide polymorphism in the catalase gene may interfere with the enzyme's subunit assembly and function, and is more frequent among vitiligo patient.⁽⁵⁰⁾ Reactive oxygen species (ROS) and H₂O₂ in excess can damage biological processes through oxidative mechanisms with limited ability for repair due to H₂O₂ excess compounding the damage, and this situation has been documented in vitiligo. The resultant protein and lipid damage could be sufficient with its own to initiate melanocytic failure, but another effect of oxidation could be to initiate melanocyte failure and apoptosis leading to uptake by Langerhans cells or DCs and if these Langerhans cells or DCs become activated, they may trigger melanocytes reactive immune response that can eradicate melanocytes in the skin leading to

depigmentation. This immune response principally involves cytotoxic T-cells.⁽⁵¹⁾ In addition to the failure of the regulatory T cell mechanisms that was mentioned earlier allows the process to continue indefinitely, in keeping with the chronic, relentless course of generalized vitiligo.^(52,43)

BIOCHEMICAL FACTORS

The biochemical theory states that the dysregulation of biopterin pathways predisposes to melanocyte cytotoxicity and vitiligo.⁽⁵⁾ Pteridines (6R)-L-erythro5,6,7,8 tetrahydrobiopterin (6BH4) and (7R)-L-erythro5,6,7,8 tetrahydrobiopterin (7BH4) are elevated in vitiligo. 6BH4 is an essential cofactor for phenylalanine hydroxylase, the enzyme that converts dietary phenylalanine to tyrosine. Increased 6BH4 drives the metabolic pathway forward leading to accumulation of byproducts 7BH4 and H₂O₂.⁽⁵²⁾ Increased 7BH4 inhibit phenylalanine hydroxylase, further contributing to an increase of 6BH4, which is cytotoxic in high concentration.⁽⁵³⁾

MELANOCYTORRHAGY HYPOTHESIS

This hypothesis proposes that melanocytes are weakly anchored and minor friction and/or other stress can induce upward migration and loss of melanocytes⁽¹⁵⁾ and this theory is thought to be of relevance in Koebner phenomenon and vitiligo lesions over trauma sites. Tenascin, an extracellular matrix molecule which inhibits adhesion of melanocytes to fibronectin, is elevated in vitiliginous skin, and may contribute to loss of melanocytes or ineffective population.⁽⁵⁴⁾

DECREASED MELANOCYTE SURVIVAL HYPOTHESIS

This theory suggests a deficiency in the survival signals of melanocytes which leads to its apoptosis. Keratinocyte-derived stem cell factor regulate melanocyte growth and survival by binding to membrane tyrosine kinase receptor c-Kit. The significantly decreased number of c-Kit receptors in perilesional melanocytes⁽⁵⁵⁾ and the lower expression of stem cell factor from surrounding keratinocytes⁽⁵⁶⁾ may contribute to vitiligo pathogenesis.

CLASSIFICATION OF VITILIGO

The classification of vitiligo proposed by Picardo and Taieb (Table 1)⁽¹⁾.

Focal vitiligo may evolve into SV, into NSV, or may remain unclassifiable based on the NSV/SV paradigm.

Table 1. Classification of vitiligo Picardo and Taieb¹.

Type of vitiligo	Subtypes	Remarks
Non-segmental (NSV)	(focal) ^a , mucosal, acrofacial, generalized, universal	Subtyping may not reflect a distinct nature, but useful information for epidemiologic studies
Segmental vitiligo (SV)	Focal ^b , mucosal, unisegmental, bi- or multisegmental	Further classification according to distribution pattern possible, but not yet standardized
Mixed (NSV + SV)	According to severity of SV	Usually the SV part in mixed vitiligo is more severe
Unclassified	Focal at onset, multifocal asymmetrical non-segmental, mucosal (one site)	

^aPossible onset of NSV.

^bSee text for discussion.

Focal vitiligo refers to an acquired, small, isolated hypopigmented lesion that does not fit into a typical segmental distribution, and which has not evolved into NSV after a period of 1–2 years.^(1,57)

SV is defined descriptively as for NSV except for a unilateral distribution ("asymmetric vitiligo") that may totally or partially match a cutaneous segment such as a dermatome, but not necessarily. Other distribution patterns of SV can be encountered that cross several dermatomes or correspond to large areas delineated by Blaschko's lines. Some specific features exist such as rapid onset and hair follicle pigmentary system involvement. One unique segment is involved in most patients, but two or more segments with ipsi- or contralateral distribution is involved in rare patients.⁽¹⁾

Regarding segmental vitiligo (SV) and non-segmental vitiligo (NSV), it was found that both disease entities have distinct clinical characteristics. Compared to SV, NSV in pediatric patients was associated with higher number of lesions and larger body surface area of involvement. There was a higher incidence of the Koebner phenomenon in NSV and more frequent progression of the disease. Thyroid abnormalities and hyperpigmented rim around vitiligo lesions were observed only in NSV.⁽⁵⁸⁾ One interesting study divided SV into different phenotypes based on a clinical observational study. These different phenotypes include: unilateral segmental type, bilateral segmental type, and mixed segmental and generalized type. Furthermore the lesions were examined to check if it was associated with halo nevi or not. Based on these clinical observations, the mixed type, the coexistence with other autoimmune diseases and halo nevi in some patients, as well as the family history of NSV pointed towards a possible

aetiopathological overlap between SV and NSV. Whether different aetiopathological mechanisms underlie the different clinical phenotypes of segmental vitiligo remains to be elucidated.⁽⁵⁹⁾

It worth to mention in this context that the Vitiligo European Task Force (VETF) convened a consensus conference on issues of global importance for vitiligo clinical research during the 2011 International Pigment Cell Conference (IPCC) and one of the topics they discussed is the revision of the classification of vitiligo. VETF used the classification of Picardo⁽¹⁾ and Taieb for their work and a consensus emerged that segmental vitiligo be classified separately from all other forms of vitiligo and that the term 'vitiligo' be used as an umbrella term for all non-segmental forms of vitiligo, including 'mixed vitiligo' in which segmental and non-segmental vitiligo are combined and which is considered a subgroup of vitiligo.⁽⁵⁷⁾

Consensus statements and classification: The term 'vitiligo' (V) is the recommended umbrella term for all non-segmental forms of vitiligo. As a transition, vitiligo/NSV can be used. Segmental vitiligo refers to a clinically unambiguous segmental distribution of depigmented lesions, typically associated with rapid onset and with leukotrichia. There is no consensus concerning the mechanism underlying lesion distribution in SV. Mixed vitiligo, being the coexistence of SV + V, is a subgroup of vitiligo. Focal vitiligo, a term that applies to localized macules characterized by loss of melanocytes, is assigned to the category unclassifiable vitiligo until more definitive classification can be made on clinical grounds (generally after 1 – 2 years of follow-up). Cases with long-lasting focal lesions or of pure mucosal vitiligo, if not classified as SV, may remain 'unclassifiable'.⁽⁵⁷⁾

ASSOCIATIONS

VITILIGO AND AUTOIMMUNITY

An epidemiological study was done on young Italian males of about eighteen years old who were called for the national compulsory service in the Italian Navy. Forty patients with the diagnosis of vitiligo underwent blood tests including search for autoantibodies. Circulating autoantibodies were detected in 42.5% of subjects. Anti-thyroglobulin antibodies were documented in 27.5%, anti-thyroperoxidase in 22.5%, anti-smooth muscle in 17.3%, anti-nuclear, anti-mitochondrial and anti-gastric parietal cells in 2.5% respectively. Only in two cases (5%) an overt thyroid disease was diagnosed. Circulating autoantibodies (particularly anti-thyroid antibodies) were statistically associated with a lower duration of the disease.⁽⁶⁰⁾

A study from Turkey investigated 80 patients with the diagnosis of vitiligo clinically, laboratory findings as well as auditory abnormalities and the association of other autoimmune disorders. Vitiligo vulgaris was the most common type, followed by focal, acrofacial, segmental and universal types. Forty-four (55%) patients had an associated autoimmune disease. Hashimoto thyroiditis was associated in 31%, alopecia areata in 12.5%, pernicious anemia in 8.7%.⁽⁶¹⁾

AUDIOLOGICAL ASSOCIATIONS

Auditory problems were observed in 20 (37.7%) patients from the previously mentioned study,⁽⁶¹⁾ where nine of them with unilateral minimal hearing loss while the other 11 patients with bilateral hearing loss over a large range of frequencies (2000-8000Hz). This study necessitates the audiological examination of all patients with vitiligo for auditory problems which commonly presents as hypoacusis. In addition to the aforementioned study, another study from Turkey performed conventional pure-tone and high-frequency audiometric tests and pure-tone average hearing thresholds were calculated for 22 patients with vitiligo and 22 age and sex matched controls.⁽⁶²⁾ Transient evoked otoacoustic emission testing (TEOAE) was also performed. Hearing thresholds at pure-tone and high-frequency audiometry were higher in patients with vitiligo. Also significantly lower high-frequency amplitudes were recorded during transient evoked otoacoustic emission testing in the disease group.⁽⁶²⁾ In this context, it is known that melanocytes are derived embryonically from the neural crest and are located in

the epidermis, hair bulbs of the skin, uveal tract and retinal pigment epithelium of the eye, inner ear and leptomeninges.⁽⁶³⁾ Melanocytes in the stria vascularis of the inner ear are believed to be required for normal development of the cochlea,⁽⁶⁴⁾ and the development and/or maintenance of the endocochlear potential EP.⁽⁶⁵⁾ So, hearing impairment in patients with vitiligo may be due to destruction or loss of function of inner ear melanocytes as well as melanocytes of the skin, and further studies in this area are warranted.

CHOROIDAL ASSOCIATIONS

One more area of affection is the pigmented choroid, one study demonstrates four patients with a diagnosis of primary idiopathic choroidal vitiligo which presents as flat pigmentation involve large segments of the posterior choroid, leaving only residual patches of choroid pigment in patients with cutaneous vitiligo; these patients were referred to the authors as having large choroidal nevi.⁽⁶⁶⁾ Primary choroidal vitiligo occurs as an idiopathic process without preceding inflammation, toxins, or trauma. Secondary choroidal vitiligo is generally post-inflammatory and found most often with Vogt-Koyanagi-Harada VKH syndrome. VKH Syndrome is an autoimmune reaction to epidermal, cochlear, meningeal, and uveal melanin resulting in destruction of the melanin-producing cells and producing cutaneous vitiligo, tinnitus, headache, and choroid depigmentation and atrophy, classically with extensive overlying retinal pigment epithelial RPE changes.^(67,68)

VITILIGO AND INTERFERON (SYSTEMIC AND LOCAL ASSOCIATIONS)

A recent study reported eight cases of vitiligo appeared after treating HCV with interferon (IFN),⁽⁶⁹⁾ Vitiligo has been reported in patients treated with IFN for HCV, HBV, melanoma, and CML.⁽⁷⁰⁻⁷⁵⁾ Few patients have been reported with vitiligo at the injection sites of IFN in patients with chronic viral hepatitis C.^(76,77) The development of vitiligo in these patients is believed to be biological effects of IFN, most probably by induction of antimelanocyte antibodies or by activation of the cells of the cellular mediated immune response particularly the cytotoxic T cells against melanocytes. It is believed that IFN unmask vitiligo in susceptible patients rather than causing it.

VITILIGO AND VITAMIN D

A pilot study was performed to assess the role of 25-hydroxyvitamin D levels in patients with vitiligo

vulgaris. 25-Hydroxyvitamin D levels were divided into: normal (> 30 ng/ml), insufficient (< 30 ng/ml) and very low level (< 15 ng/ml). Insufficient 25-hydroxyvitamin D levels were associated with increasing Fitzpatrick phototypes and very low 25-hydroxyvitamin D levels were associated with comorbid autoimmune illness and authors considered very low 25-Hydroxyvitamin D levels to be a reasonable screening tool for the presence of comorbid autoimmunity.⁽⁷⁸⁾ Based on data from this study, Silverberg NB included testing of the 25-hydroxyvitamin D level at the time of disease diagnosis among a suggested a list of laboratory evaluations for children with vitiligo vulgaris and stated that very low levels below 15 ng/ml should trigger more extensive autoimmune evaluations.⁽⁷⁹⁾

DIAGNOSIS AND TREATMENT OPTIONS

The diagnosis of vitiligo is based mainly on clinical examination, however, there is a list of differential diagnoses that should be in mind if the diagnosis is uncertain. Table 2 shows the possible differential diagnosis of vitiligo.

In case of uncertain diagnosis, in addition to clinical assessment, noninvasive and invasive procedures may be needed (Table 3).

In the assessment steps and before starting treatment, it is important to consider the age of the patient, duration of the disease, the course of the disease (progressive, regressive or stable during the last 6 months), type or subtype of vitiligo (as some types or subtypes may necessitate specific treatment approaches), associated diseases in particular autoimmune diseases, previous medication and if possible the psychological profile of the patient or Global Quality of Life QoL assessment.^(80,1)

TOPICAL CORTICOSTEROIDS

As first-line treatment of limited forms of vitiligo, TCS and topical calcineurin inhibitors (TCI) are now widely used.⁽⁸¹⁾ Topical corticosteroids have the best results (75% of repigmentation) on sun-exposed areas (face and neck),^(82,83) in dark skin,⁽⁸⁴⁾ in recent lesions⁽⁸⁵⁾ and in children compared to adults.⁽⁸⁶⁾

Based on comparative studies between topical corticosteroids and topical calcineurin inhibitors, topical corticosteroids had an equivocal to slightly higher rates of repigmentation.^(87,88)

Table 2. Differential diagnosis of vitiligo^{1,57}.

Inherited or genetically induced hypomelanoses(usually present at birth) Piebaldism Tuberous sclerosis Ito's hypomelanosis Waardenburg's syndrome Hermanski-Pudlak syndrome Menkés syndrome Ziprkowski-Margolis syndrome Griscelli's syndrome
Post-inflammatory hypomelanoses Related to an increased epidermal turn over Psoriasis Atopic dermatitis Related to an acute lichenoid/cytotoxic infiltrate with pigment incontinence Lichen planus Toxic drug reaction
Para-malignant hypomelanoses Mycosis fungoides Melanoma-associated depigmentation
Para-infectious hypopigmentation Pityriasis versicolor Leprosy Leishmaniasis Onchocerciasis Acquired macular hypomelanosis
Post traumatic leucoderma Post-burns Post-scars
Melasma Occupational and drug induced depigmentation Phenolic-catecholic derivatives Systemic drugs(chloroquine, fluphenazine, physostigmine, imatinib) Topical drugs (imiquimod, long-term use of topical steroid)

Local side-effects of potent or very potent topical corticosteroids are well known including epidermal atrophy, telangiectasia, striae distensae, steroid folliculitis and side effects associated with systemic absorption.^(89,87)

Currently, there are no studies available on optimal duration of topical corticosteroids therapy and on discontinuous applications that could improve the therapeutic index.⁽⁸¹⁾

TOPICAL CALCINEURIN INHIBITORS TCIS

The beneficial effects of TCIs have been reported in the treatment of vitiligo since 2002, particularly in

Table 3. Recommended diagnostic procedures in vitiligo⁵⁷.

If diagnosis is certain	If diagnosis is uncertain
Anti-TPO, antithyroglobulin antibodies TSH and other tests if needed to assess thyroid function or diagnosis (e.g. anti-TSHR antibodies if Grave's disease) Additional autoantibodies (only if patient's history, family history, and/or laboratory parameters point to a strong risk of additional autoimmune disease), endocrinologist/immunologist advice if multiple autoimmune syndrome detected	Punch biopsy from lesional and non-lesional skin Other tests if needed (mycology, molecular biology to detect lymphoma cells, etc.)

TPO, thyroid peroxidase; TSH, thyroid stimulating hormone; TSHR, TSH receptor.

areas where prolonged use of topical potent corticosteroids is contraindicated.⁽⁹⁰⁾ Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are topical immunomodulators; calcineurin is an intracellular protein in lymphocytes and dendritic cells and it acts as transcription factor for cytokines, such as IL-2, TNF α .⁽⁹¹⁾

As mentioned earlier in the etiology section, patients with vitiligo have increased levels of IL-10, TNF α , and INF γ .⁽¹⁷⁾ Treatment with tacrolimus decreases tissue counts of TNF α 1 and enhances melanoblasts migration and differentiation.⁽⁹²⁾

Few randomized studies have been published, showing beneficial results mainly in the head and neck region, and in both children and adults.^(93,94) It seems like the use of TIMs in the treatment vitiligo enhances the effect of light and/or laser (308 excimer laser) therapy.^(95,96)

Occlusive treatment may enhance the effect on arm and leg lesions that were previously non-responsive to therapy.^(97,98)

Twice-daily applications of 0.1% topical tacrolimus has shown more efficacy than once-daily applications.⁽⁹⁹⁾

Like what was previously mentioned in the treatment of vitiligo with topical corticosteroids, the information about the ideal treatment period and usefulness of long-term vs. intermittent use is not available.

PHOTOTHERAPY

Photochemotherapy with psoralen plus UVA radiation (PUVA) combines the use of psoralen with long-wave (320–340 nm) UVA radiation, photochemotherapy with khellin plus UVA (KUVA) combines the use of

khellin with long-wave (320–340 nm) UVA radiation, photochemotherapy with L-phenylalanine (L-phe) combines the use L-phe with UVA (PAUVA) or UVB, 311 nm narrow band UVB (NB-UVB) phototherapy, and laser therapy (targeted phototherapy devices) including: 308 nm excimer laser (MEL), Bioskin laser which transmits focused 311 nm wave length, helium neon laser (HeNe) which transmits 632.8 nm wavelength.

Narrow band UVB radiation currently represents the phototherapy of choice for active and/or widespread vitiligo.⁽⁸⁰⁾ Side effects are less frequent than in PUVA especially regarding the risk of melanoma and non-melanoma skin cancers,⁽¹⁰⁰⁾ and the efficacy is at least equivocal.^(101–103)

Oral KUVA has been largely abandoned due to significant liver toxicity.⁽⁸⁰⁾

LASER THERAPY (TARGETED PHOTOTHERAPY)

Monochromatic excimer laser (MEL) 308 nm

MEL is the best-studied and most popular targeted phototherapy for the treatment of vitiligo with less total body irradiation, and less side effects on normal skin. MEL is used one to three times weekly for an initial course of 12 weeks and is approved by the FDA for treating vitiligo.⁽¹⁰⁴⁾ The outcome of the treatment with MEL is improved if it is combined with other treatment modalities, such as topical hydrocortisone 17-butyrate,⁽¹⁰⁵⁾ topical tacrolimus.⁽¹⁰⁶⁾ The benefit of combining topical vitamin D3 analogs is not clear but topical tacalcitol may induce earlier repigmentation, requiring less cumulative radiation, and it may not affect the final repigmentation.^(107,108)

Bioskin

Bioskin is a new device which transmits a focused 311-nm UVB radiation, Bioskin phototherapy (monotherapy) had repigmentation rates of more than 75% in 72% of patients and better results were achieved if it was combined with other treatment modalities. The best result was achieved if combined with betamethasone dipropionate.⁽¹⁰⁹⁾

Helium neon laser

The helium neon (HeNe) laser emits 632.8 nm radiation and is used for the treatment of segmental vitiligo. It modifies adrenergic dysregulation of cutaneous blood flow seen in SV,⁽¹¹⁰⁾ and promotes melanogenesis, melanocyte growth, migration and survival in the skin.^(111,112)

ORAL STEROID MINIPULSE THERAPY

Pulse therapy refers to intermittent administration of large (suprapharmacological) doses to enhance the therapeutic effect and reduce the side effect of particular drug.⁽⁸⁰⁾ Oral minipulse of moderate doses of betamethasone/dexamethasone has been pioneered in India by Pasricha et al.⁽¹¹³⁾ Systemic steroid can arrest the effect of the disease^(115–117) but are not effective in repigmentation; moreover the side effects of long-term use of systemic steroids contraindicate their common use.⁽⁸⁰⁾

ANTIOXIDANTS

Oral antioxidant

Oral antioxidant supplementation could be useful in the treatment of vitiligo and the rationale for their use is to counteract the occurrence of cellular oxidative stress.⁽¹¹⁸⁾

Monotherapy with oral ginkgo biloba significantly decreased disease progression compared to placebo, in a double-blind placebo-controlled trial,⁽¹¹⁹⁾ also, in a double-blind placebo-controlled trial a mixture of alpha lipoic acid, vitamin C, vitamin E and polyunsaturated fatty acids improved repigmentation rates and promoted dose reduction of narrow band-UVB.⁽¹²⁰⁾

Oral polypodium leucotomos significantly improved the repigmentation rates when combined with narrow band UVB phototherapy on the head and neck.⁽¹²¹⁾

Randomized control trials (RCTs) evaluating systemic antioxidant supplementation provide a limited evidence of efficacy, and further confirmation is needed before recommending their prescription in vitiligo.⁽⁸⁰⁾

Topical antioxidants

Catalase and superoxide dismutase are enzymes with antioxidant properties⁵. Some studies showed noticeable repigmentation response either as monotherapy or in combination with phototherapy,^(122–124) while other studies didn't show such benefit.^(125,126)

SURGICAL THERAPY

Surgical therapy includes: blister graft (BG), split-thickness skin graft (STSG), punch graft (PG), and autologous melanocyte suspension transplant (AMST).

The BG technique is used to create donor epidermal graft tissue. This technique creates a subepidermal bulla at the donor site, from which the roof is surgically removed and transplanted into the recipient site. It gives very good cosmetic results, but it is not suitable for large lesions.^(127,128)

In STSG, the graft is harvested with the assistance of dermatome which creates a graft of uniform thickness; it can be meshed to cover a large surface area, placed over dermabraded recipient site, and dressed with gauze.⁽¹²⁹⁾ This technique gives remarkable repigmentation response.⁽¹³⁰⁾ Compared to BG, the STSG can cover a greater surface area, with even higher percentages of repigmentation.⁽¹³¹⁾ Phototherapy enhances repigmentation in both techniques.^(132,133)

PG is the easiest and least expensive surgical technique in treatment of vitiligo. Punch grafting showed good repigmentation and cosmetic result in one of the largest studies, performed in 1000 patients with vitiligo.⁽¹³⁴⁾ Phototherapy may enhance the repigmentation especially NB-UVB.⁽¹³⁵⁾ However, it is not suitable for large surface area.

The idea of the AMST technique is to harvest tissue from donor site by any technique such as, BG, PG, STSG, curettage); release them into a suspension, and then transplant them into de-epithelized recipient skin.⁽¹³⁶⁾ The rate of repigmentation and cosmetic results with this technique is promising.^(137,138)

However the types of surgical interventions mentioned are not without side effects, which include scarring, infection and hyperpigmentation.^(139,140)

Surgical technique is not advised for patients who have tendency to koebnerize as it will induce depigmentation in both donor and recipient sites.⁽¹⁴¹⁾ The most common side effect associated with PG



Figure 1. Treatment algorithm for vitiligo. The treatment order was determined by the level of evidence in the literature for each treatment⁵.

is cobblestoned texture with the grafts raised in comparison to the surrounding skin.^(139 – 141)

Surgical treatment should be reserved for patients with stable (a period of disease inactivity ranging from six months to two years) recalcitrant vitiligo who

failed to respond to non-surgical treatment and with no history of Koebner's phenomenon. The best indications for surgical techniques are stabilized SV or focal vitiligo, mainly with leucotrichia and large lesion areas.⁽⁸⁰⁾

CAMOUFLAGE

Considering the psychological burden of the disease on the patient's body image, especially with lesions on the face, neck, and hands, camouflage considered an important part of the treatment of vitiligo and should be recommended to be used at all stages of treatment.^(142–146)

Products developed to disguise skin disfigurement and require specialized application techniques.^(142–144) It can be temporary such as, make up (compact, liquid and stick foundation, etc.), semi-permanent such as, self-tanning agents, or permanent, such as micro-pigmentation and tattoos.⁽¹⁴⁵⁾ Permanent camouflage should be considered with caution due to the unpredictable course of vitiligo.⁽¹⁴⁶⁾

DEPIGMENTATION

In patients with extensive vitiligo with remaining pigmented islands of normal skin or patients with refractory vitiligo when satisfactory repigmentation is not attainable, depigmentation may provide pleasing cosmetic outcomes. Monobenzone ethyl ester (MBEH) is a derivative of hydroquinone (HQ), unlike hydroquinone, MBEH almost always causes irreversible depigmentation.^(147,148) The Q-switch ruby laser has been extensively used for depigmentation in vitiligo universalis, although Q-switch Alexandrite laser is also effective.⁽¹⁴⁹⁾ Combination between topical methoxyphenol and Q-switched ruby laser has been proposed by Njoo et al.⁽¹⁴⁸⁾ and achieved complete depigmentation in 69% of patients with universal vitiligo.

PSYCHOTHERAPY

Depigmentation exerts a negative impact on the patient's appearance and self-esteem.⁽¹⁵⁰⁾ Levels of disability vary according objective factors such as, extension and site of the disease, skin type, ethnicity, and cultural background.^(151,152) Perceived severity of the disease seems to be influenced by the patient's personality more than objective factors.⁽¹⁵³⁾ Lack of a

universally effective treatment adds to the psychological burden of the disease.⁽¹⁵⁴⁾

BIOLOGICS AND IMMUNOSUPPRESSANTS

Tumor necrosis alpa inhibitors,^(155–158) immune suppressants like azathioprine,⁽¹⁵⁹⁾ cyclophosphamide⁽¹⁶⁰⁾ and cyclosporine⁽¹⁶¹⁾ were studied in the treatment of vitiligo, but the current data do not provide enough evidence to recommend their use in patients with vitiligo. Moreover, the potential side effects of these agents do not justify their use in vitiligo.⁽⁸⁰⁾

ALTERNATIVE AND HERBAL TREATMENT

Alternative treatments like herbal and natural products have been used also in vitiligo, example of this kind of treatment is Placentrx[®] which is a topical human placental extract.^(162,163)

As stated in the Cochrane review on vitiligo⁽¹⁶⁴⁾ there are many limitations to deriving a valuable algorithm of treatment for all patients with vitiligo based on RCTs. Firstly, RCTs are rare and often lacking important methodological steps or details. Secondly, studies have often been conducted in heterogeneous groups in terms of duration or progression, and mixing localized, segmental and non-segmental forms. Thirdly, there are many confounding factors (light exposure in long-term interventions, nutritional intake of antioxidants, or awareness of the limitation of the Koebner phenomenon).

At last, it is worth to mention that standardization of the disease severity assessment tools and response to treatment should be unified in all future studies to be able to merge data from small clinical trials and do good meta-analyses review of efficacy of different available treatment modalities.

Treat algorithm which divides the treatment options into first-, second-, third-, fourth lines of therapies are summarized in Figure 1; the treatment order was determined by the level of evidence from the literature for each treatment.⁽⁵⁾

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