Vitiligo: What's old, what's new

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Abstract

Vitiligo is an acquired pigmentary disorder afflicting 0.5-2% of the world population for both sexes and all races with a capricious and unpredictable course. It has a complex etiology and varies in its manifestation, progression and response to treatment. Even if the precise aetiology and pathobiology of the disease are complex and still debated, recent evidence supports that vitiligo is a T CD8+ cell-mediated autoimmune disease triggered by oxidative stress. To date no clinical, biological and histological criteria allow us to establish the prognosis with certainty. The choice of the best therapy for adult and childhood vitiligo is based on various factors, such as the patient's age, psychological condition and expectations, distribution and extension of skin lesions, type of vitiligo (stable or not) and availability and cost of therapeutic options. Since vitiligo has a deep psychological impact on patients and their quality of life, treating the disease is very important. As dermatologists, we have important goals in the treatment of vitiligo patients: stabilization of the disease progression, repigmentation of the lesions and especially the persistence of the aforementioned repigmentation. Although several medical and surgical therapeutic options have been proposed, no definite cure has yet been developed and the long-term persistence of repigmentation is unpredictable. We review the different therapeutic options with particular attention on the recurrence rate.

Introduction

Vitiligo is an acquired pigmentary disorder afflicting 0.5-2% of the world population for both sexes and all races with a capricious and unpredictable course.[1]

Clinically it is characterized by sharply demarcated, variably shaped depigmented macules surrounded by normal skin which can affect any body or mucous area, but which commonly appear on the face, dorsa of the hands, nipples, axillae, umbilicus and sacral, inguinal and anogenital regions with an important psychological impact for the patient.

It can be classified as segmental or non-segmental (localized or generalized) considering the clinical involvement and stable or progressing depending on the activity of the disease.[2]

Even if the precise aetiology and pathobiology of the disease are complex and still debated, recent evidence supports that vitiligo is a T CD8+ cell-mediated autoimmune disease triggered by oxidative stress.[3] Different hypotheses have been suggested to explain the melanocyte loss and studies have shown that vitiligo is a multifactorial, polygenic autoimmune disorder that occurs in only a minority of genetically susceptible individuals and is therefore believed to have a strong component of environmental triggering.[4] The association with autoimmune disorders and organ-specific antibodies as well as the fact that repigmenting therapies have immune-modulating effects indirectly support the idea of an autoimmune pathogenesis of the disease.[5]

Patients with vitiligo and their first-degree relatives have a higher incidence of other autoimmune conditions (including thyroiditis, pernicious anemia, Addison's disease, systemic lupus erythematosus and inflammatory bowel disease) than the general population, besides a personal and familial association with canity,[6] atopic dermatitis,[7,8] rheumatoid arthritis, types 1 and 2 diabetes mellitus, alopecia areata, psoriasis, chronic urticaria, lichen sclerosus, celiac disease, systemic lupus erythematosus and sarcoidosis.

A large extent of the disease and increasing years with vitiligo are the factors most related with associated autoimmune disease.[9,10]

It has also been proposed that two major pathomechanisms are related to autoimmune vitiligo: an antibody-based dominant in diffuse vitiligo and a T-cell-based dominant in the localized disease.[11]

Different circulating antibodies to melanocytes, which are uncommon in healthy individuals, have been found in the sera of vitiligo patients. These seem to be related to the extent of the disease: they are present in more than 90% of the patients with greater depigmentation and in 50% of subjects with minimal lesions.[12]

Characterization of these antibodies has demonstrated that they belong to the IgG class. Interestingly IgG and C3 deposits have also been sporadically observed in the basal membrane zone of lesional skin, which correlates with the observation that the binding of IgG to cultured melanocytes increases with disease activity and extent. Furthermore, studies have found that IgA levels of anti-pigment cell membrane antibodies are associated with disease activity, suggesting a close relationship with anti-melanocyte IgA antibody levels.[12]

The production of large amounts of melanin increases the risk of misfolding of those proteins, which activates a stress pathway within the cell called the unfolded protein response. In addition, this process generates reactive oxygen species from mitochondrial energy metabolism. These two pathways appear to be hyperactivated in melanocytes from vitiligo patients, suggesting that these cells are less able to tolerate the demands of melanin production than those from healthy individuals. Once melanocytes become stressed, they release inflammatory signals that activate innate immunity, which may represent the initiating

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event in vitiligo. Studies report that different cells, including macrophages, dendritic cells, natural killer cells and Langerhans cells are involved.[13]

Furthermore, there is a genetic predisposition in a polygenic pattern with multifactorial inheritance. Genome-wide association studies identified approximately 50 vitiligo-associated genes. The overwhelming majority of these genes are immune genes, confirming a critical role for the immune system in vitiligo pathogenesis. They include genes critical for antigen presentation, T-cell development, T-cell receptor signaling, T-cell activation, melanocyte homeostasis and melanogenesis, and apoptosis.[14]

To date no clinical, biological and histological criteria allow us to establish the prognosis with certainty, although segmental vitiligo is described as less common, frequently associated with leukotrichia and less responsive to treatment than other variants.[3]

The choice of the best therapy for adult and childhood vitiligo is based on various factors, such as the patient's age, psychological condition and expectations, distribution and extension of skin lesions, disease activity and availability of therapeutic options.

Since vitiligo has a deep psychological impact on patients and their quality of life, treating the disease is very important. Treatment goals include: stabilization of the disease progression, repigmentation of the lesions and especially the persistence of the aforementioned repigmentation.[15]

Although several medical and surgical therapeutic options have been proposed, no definite cure has yet been developed and the long-term persistence of repigmentation is unpredictable.[16]

We review the different therapeutic options with particular attention on the recurrence rate.

Phototherapy

Psoralen UVA and narrow-band UVB therapy

Phototherapy, including PUVA and NBUVB, has been established over the past few years and still represents the principal treatment for generalized vitiligo. Since 1948 PUVA has been used with success but in the last 30 years it has been supplanted by NBUVB which showed superior safety and efficacy. The lack of photosensitizer, the lower cumulative dose, the fewer adverse effects as well as a superior efficacy are considered the major advantages. NBUVB phototherapy is useful in early active vitiligo in order to halt disease progression and to stimulate repigmentation in stable vitiligo. In fact, different studies have reported repigmentation rates ranging from 40% to 100%.

Several variables can influence the repigmentation: the location of the lesions, the age of vitiligo, type of vitiligo, skin phototype and number of treatments, as well as patient motivation. The most effective response is visible on face and neck, whereas hands and feet show minimal response. The duration of the disease is reported to be inversely related with repigmentation percentage suggesting progressive exhaustion of melanocyte storage in the outer root sheath and that follicular melanocytes are destroyed during the disease process. Furthermore, there is general agreement on the fact that non-segmental vitiligo usually responds better and that darker skin types can predict a good response.[17]

Even if a universally accepted protocol for NBUVB is not available, it is described as optimal to start at a safe, low dose 2 to 3 times per week with 10% to 20% dose increments. Long treatment duration for several months to years can result in poor compliance but it is reported to enhance the treatment response, and a period of at least 6 months is required to assess the responsiveness.[18]

Follow-up data on patients after NBUVB are limited and only few studies report the recurrence rate,[19] which is interestingly described as variable between 45% and 55% in 1-2 years in western populations.[20,21]

Analysis of 150 Indian patients showed that a majority of cases, about 73, achieved 25-75% repigmentation, with an average of 51±19 exposures. Only 3 patients developed depigmentation of repigmented sites during 6 months follow-up confirming a better response in darker skin types.[22]

A recent Thay study evaluated a persistent repigmentation in 80% of 57 patients at 1 year after cessation of phototherapy.[23]

While the mechanisms of action are the same as classical phototherapy, targeted phototherapy acts in a more precise way because by treating only vitiliginous patches, the operator can use a more

appropriate dose of energy, leading to shorter duration and less frequent treatment sessions.

Excimer is preferred for small areas, whereas NBUVB is more useful for widespread vitiligo.

To enhance results phototherapy can be combined with various medications (topical calcipotriol, topical calcineurin inhibitors, systemic antioxidants).[24]

Excimer laser 308 nm

Due to its selectivity and pro-pigmentary properties, the 308-nm excimer laser represents the latest advance in the concept of selective phototherapy for vitiligo.[25] When compared with standard phototherapy, the 308-nm xenon-chloride excimer laser has the advantage of better precision (spot size is variable from 14 to 30 mm) and the ability to deliver higher energy fluences to the target tissue in less time. It is also possible to selectively move the beam of light and thus treat the specific area involved, sparing healthy skin and limiting the unsightly tanning of perilesional skin in vitiligo patients which is commonly observed with other phototherapies. By contrast disadvantages include that is impractical for treating large surfaces and that purchase and maintenance costs of these devices are rather expensive.[26]

Spencer *et al*.[27] demonstrate that vitiligo patches treated with 308-nm excimer laser repigmented in less time than that required with current methods, in fact pigmentation start after only five sessions and increase with continuation of treatment. Among the factors that can influence the clinical response to treatment, seems to play a crucial role localization of the lesions.

Taneja *et al*.[28] report repigmentation of at least 75% in all the lesions located on the face vs. none on the hands and feet. The repigmentation rate seems to be linked to the total number of sessions and not to their frequency. It is difficult to know if repigmentation is stable with time because the follow-up of existing series is short or non-existent. Passeron *et al*.[29] report that in their series about 15% of new depigmentation is observed 1 to 3 years after the end of treatment. Wu *et al*.[30] used a 308-nm excimer laser twice to three times weekly and compared it with 0.1% tacrolimus ointment twice daily in patients with stable and active vitiligo for a duration of 6 months. In the stable vitiligo group, the excimer laser provided a superior response rate to topical tacrolimus after 3 months (41% *vs*. 10% achieving >50% repigmentation) and 6 months (48% *vs*. 35%) of treatment. In patients with active lesions, intramuscular betamethasone injection was added monthly for 3-6 months combined with tacrolimus or excimer laser. Similarly, the excimer laser showed a superior response at 3 months (56% *vs*. 38%) and 6 months (81% *vs*. 50%).

The XeCl excimer laser is the strongest inducer of apoptosis in T cells resulting in an intense pro-apoptotic effect on them. Zhang *et al*.[31] demonstrated that the 308-nm

excimer laser is effective in reducing the infiltration of CD4+ and CD8+ T cells but promotes the infiltration Treg cells and the secretion of TGF-β and IL-10 in the lesion skin of non-segmental vitiligo patients, especially in the stable stage.

Medical therapy

Corticosteroids

Corticosteroids reduce the cellular immune response and melanocyte destruction, while inducing melanocyte regeneration and melanin production.[32]

Topical corticosteroids are the mainstay of treatment for localized vitiligo; in particular high- and mid-potency corticosteroids are applied once and twice daily respectively. Agents with negligible systemic or local side effects, such as mometasone furoate, are usually preferred.[33] They showed to have a reservoir effect that lasts for around 5 days and the risk of development of cataracts and glaucoma in patients using periorbital topical corticosteroids was not found to be raised in case-control studies.[34] Systemic corticosteroids represent the first-line therapy for the stabilization of the rapidly progressive disease. Oral mini-pulse (OMP) therapy (administration at suprapharmacological doses for 2 days/week) has been especially used to reduce adverse effects.[35] Effective long-term use of steroids may cause striae, atrophy, tachyphylaxis, telangiectasias, acneiform eruptions (topical) and hyperglycemia, hypertension, osteoporosis, Cushing's syndrome, and suppression of hypothalamo-pituitary-axis (systemic).[32]

The study by Kanwar *et al*.[36] on 444 patients treated with OMP dexamethasone 2.5 mg twice weekly for a maximum of 6 months resulted in an arrest of disease activity in 91.8% of them, with different rates of repigmentation (from minimal to excellent). Only 12.3% of the patients experienced one or two episodes of relapse: the mean disease-free survival (DFS) until the first relapse was 55.7±26.7 weeks and the mean DFS until the second relapse was 43.8±7.2 weeks.

Janus Kinase inhibitors

Janus kinase-signal transducer and activator of transcription (JAK/STAT) is an intracellular pathway that drives downstream signaling of several proinflammatory pathways. Once a cytokine binds to its receptor, JAK is activated and in turn activates STAT. The latter then acts as transcription-activators of multiple mediators. In particular JAK located inside keratinocytes is activated by IFN-gamma, then STAT activates the transcription of genes such as CXCL9 and 10 that are potent chemokines. The result is a further recruitment of cytotoxic T-cells producing more IFN-gamma that directly inhibits melanogenesis, induces senescence of melanocytes and promotes the release of heat shock protein −70 which marks the melanocytes for damage by innate immune response.[37]

A recent study showed that JAK1 and JAK3 are upregulated in vitiliginous skin probably contributing to the pathogenesis of the disease, thus selective JAK3/1 inhibition may be a favorable treatment option for these patients.[38] The JAK inhibitors that have been used in vitiligo are tofacitinib and ruxolitinib. Tofacitinib has been used at a dose of 5-10 mg twice daily orally with satisfactory repigmentation.[39] Ruxolitinib has shown good efficacy when used as a 1.5% cream twice daily on vitiligo lesions with excellent repigmentation capacity and a low side effect profile.[40] In one study, a patient with coexisting vitiligo and alopecia areata treated with ruxolitinib 20 mg twice daily had significant temporary repigmentation, which relapsed after 12 weeks.[41]

However, both tofacitinib and ruxolitinib have shown better results in photoexposed sites or in association with NBUVB therapy.[39,42]

To conclude, the cost and relative inaccessibility of JAK inhibitors, the potential adverse effects of carcinogenicity and the mixed results imply that this category is unlikely to be a major systemic treatment for vitiligo in the near future.[42] Nevertheless, further studies are needed to establish the efficacy of newer topical formulations.[39]

Calcineurin inhibitors

Topical tacrolimus (0.03 or 0.1%) and pimecrolimus (1%) are commonly employed in treating vitiligo. They are particularly preferred to topical corticosteroids for patients with limited vitiligo involving the face or areas at high risk for skin atrophy (e.g. intertriginous areas or the genitals), applied twice daily for at least 6 months.[32] They reduce pro-inflammatory cytokines and induce melanocyte growth and melanoblast proliferation.[43]

Classical immunosuppressants and immunomodulators (like Methotrexate, or systemic corticosteroids) inhibiting T-lymphocyte activation and proliferation have been successfully employed to halt the progression of the disease, while repigmentation is variably reported in different studies. However, approximately 40% of the patients relapse once these treatments are discontinued, which points towards a role of memory T-cells residing in the skin that are responsible for the relapse. Topical calcineurin inhibitors used during the periods of remission are effective in inhibiting these memory T-cells.[37]

Cyclosporine

Cyclosporine is an oral calcineurin inhibitors with a predominant immunomodulatory action which can inhibit IL-2 production and hence the activation of the T-cell pathway.

Taneja *et al*.[44] have demonstrated that Cyclosporine (at a dose of 3 mg/kg for 12 weeks) is able to halt disease progression and to induce repigmentation; in fact, it probably has also a direct effect on melanogenesis. However, large-scale controlled trials are needed to further explore its role in both progressive and stable vitiligo.

Methotrexate

Methotrexate is an antimetabolite and anti-folate drug. It results in decreased number of T-cells capable of producing TNF-alfa that has been demonstrated to be significantly higher in vitiligo lesional sites compared to perilesional, non-lesional and healthy skin. Thus, methotrexate has been tried as a steroid sparing agent in vitiligo at the dose of 10-15 mg/week orally along with folic acid supplementation.[45] Furthermore, topical methotrexate 1% gel twice daily for 12 weeks has been used in one study with significant improvement of the lesion and no local or systemic side effects.[46]

Afamelanotide

Afamelanotide is a synthetic analogue of alpha melanocyte stimulating hormone; it binds to the melanocortin-1 receptor (MC1R), stimulating melanogenesis and melanocyte proliferation.

Since MC1R is not expressed by melanocyte stem cells it has no effect on melanoblasts, thus it has been used as an adjuvant to enhance the therapeutic response to NBUVB as phototherapy induces melanoblast differentiation. Dose–response studies are required to establish optimal treatment regimens and treatment durations.[47]

Minocycline

Melanocytes in vitiligo have enhanced sensitivity to oxidative stress because of reduced expression of catalase and glutathione peroxidase, two enzymes that are known to metabolize the ROS.[11]

Exposure to stress in melanocytes leads

to a reduced expression of E-cadherin which in turn disrupts melanocyte-keratinocyte contact and so melanocytes start moving upwards in the epidermis causing the onset of apoptosis. In addition, further mechanical stress causes the removal of these melanocytes from the epidermis (melanocytorrhagy). This can explain the localization of vitiligo on sites exposed to maximum friction. Moreover, this abnormal stress response in melanocytes marks them for damage by innate immune mechanisms and perpetuates further autoimmune responses. Antioxidants administered either topically or systemically have shown promise though results are variable.[37] Minocycline has anti-inflammatory, immunomodulatory and free-radical destruction properties. It has been demonstrated that minocycline can salvage melanocytes from oxidative damage *in vitro*.[48] Its mechanism of action is complex and not completely understood; it includes inhibition of free radical and cytokine production, interference with protein synthesis, and modulation of matrix metalloproteinase activity and furthermore it has potent anti-apoptotic properties. Thus, minocycline (at a dose of 100 mg/day orally) represents a potentially powerful treatment for arresting the activity of the disease.[49]

Statins

Statins can scavenge free radicals and inhibit leucocyte chemotaxis, antigen presentation, lymphocyte activation and proliferation and block cytokine expression. Despite this, a recent randomized clinical trial failed to demonstrate that statins could provide additional benefit when administered with NBUVB.[50]

Vitamin D3 analogues

It is well known that in vitiligo there is an augmented expression of proinflammatory and proapoptotic cytokines including IL-6, IL-8, IL-10, IL-12, INF-α and TNF-α. Since Vitamin D can inhibit antigen presentation and the expression of the aforementioned cytokines, it might exert immunomodulatory effects.[51] Calcipotriol and tacalcitol are vitamin D analogues used topically, alone or combined with phototherapy, as second line therapy in vitiligo.[39] Small randomized trials evaluated their role in combination with PUVA, NBUVB, or natural sunlight for the treatment of non-segmental vitiligo with conflicting results.[52-54]

5-Fluorouracil (5-FU)

It was postulated that 5-FU could exert repigmentation by direct stimulation of melanocytes and an increase in the number of melanosomes in the keratinocytes.[55] Furthermore it can induce release of inflammatory leukotrienes C4 and D4 and an augmented production of the metalloproteinase enzyme which in turn produces a favorable environment for melanocyte migration.[39] 5-FU has been used for the topical treatment of vitiligo for a few decades and has been observed to be safe and effective in inducing repigmentation. Better results have been achieved in patients who previously underwent an epidermal abrasion (classical dermabrasion or cutaneous laser ablation) of skin lesions.[56]

Levamisole

Levamisole is an antihelminthic agent operating as a nicotinic acetylcholine receptor agonist. Furthermore, it has a wide range of immunomodulatory properties, mainly acting on macrophages and T lymphocytes, thus affecting phagocytosis, chemotaxis, adherence, and intracellular killing.[57]

It has been used in the treatment of vitiligo at the dose of 150 mg on two consecutive days orally and seems to be able to arrest the course of the disease and to induce repigmentation. The drug may be used alone, but an association with conventional therapies (*e.g.* corticosteroids) seems to be more effective.[56]

Antioxidant agents

A large variety of antioxidant agents have been used in the treatment of vitiligo alone or, more frequently, in combination with phototherapy in order to counteract the oxidative stress induced by UV itself, increasing its effectiveness.[58]

Alpha-lipoic acid is an organosulfur compound derived from octanoic acid. It is widely available as an over-the-counter nutritional supplement and has been marketed as an antioxidant. In fact, it exerts its function by increasing the level of catalase and decreasing the production of reactive oxygen species. It has been used at the dose of 50 mg twice a day orally but further studies are needed to confirm the benefit of alpha-lipoic acid supplements in the management of vitiligo.[59,60]

Ginkgo biloba has long been used in traditional Chinese medicine. The two main groups of active constituents responsible for *G.biloba*'s medicinal effects are terpene lactones and ginkgo flavone glycosides, which are present in varying concentrations in the leaf of the ginkgo tree. An *in vitro* investigation of a *G. biloba* extract documented its effect in protecting human melanocytes from hydrogen peroxide-induced oxidative stress by activating the transcription factor nuclear erythroid 2-related factor (Nrf2). Nrf2 regulates the expression of a number of genes involved in the cellular defense against oxidative stress.[61] It can be used orally at the dose of 40 mg three times daily or 60 mg twice daily.[52]

Polypodium leucotomos is a tropical fern with antioxidant and immunomodulator properties. It has been used in one randomized trial in combination with NBUVB and was shown to be more effective than NBUVB alone in inducing repigmentation of vitiligo in the head and neck.[62] Zinc is a trace element that acts as a cofactor for the enzyme superoxide dismutase, which contributes to elimination of free radicals and enhances the anti-oxidant defense mechanism. Zinc and zinc-associated glycoprotein can alter gene expression and melanin production. It has been demonstrated that vitiligo patients have lower intracelluar zinc which leads to oxidative damage and apoptosis of melanocytes. Thus, it has been used orally as zinc sulfate 440 mg per day in vitiligo patients.[59] Piperine is an alkaloid extract derived from black pepper. It seems to stimulate melanocyte replication and melanocytic dendrite generation. It is used as topical agent and is more effective when associated with low-dose UVA.[59] Pseudocatalase applied topically appears to help preventing oxidative damage similarly to catalase. Indeed, it has been demonstrated that in vitiligo patients there are low epidermal catalase levels and an accumulation of hydrogen peroxide, which in turn leads to vacuolization of epidermal melanocytes and keratinocytes caused by peroxidation.[63]

Flavonoids are polyphenolic compounds, with antioxidant, anti-microbial and anti-inflammatory properties, widely found in plants and foods (wine, beer, tea, onions, blueberries, bananas, all citrus fruits, dark chocolate and others). They have been proposed as supplements in the treatment of vitiligo. Quercetin has been especially demonstrated to protect keratinocytes and melanocytes from oxidative damage, suggesting its effectiveness as adjuvant oral therapy in vitiligo patients. Furthermore, its application may prevent ultraviolet radiation cellular damage.[56]

Green Tea polyphenols are extracts of green tea leaves, which have anti-inflammatory, antioxidant, and immunomodulatory properties, mainly because they contain Epigallocatechin-3-gallate. It can be administered both systemically and topically and may be useful for vitiligo treatment, stopping the oxidative stress of the melanocyte-unit.[64]

Prostaglandin F2 (PGF2α) analogues

Latanoprost and bimatoprost are PGF2α analogues used for glaucoma. They were found to induce skin pigmentation by increased melanogenesis thus they were used in vitiligo patients with promising results.[65,66] Recently Lotti *et al.* proposed a new protocol consisting in the association of a Fraxel Herbium laser, topical Latanoprost solution and a focused UVA1 laser which seems to provide good clinical results in term of repigmentation rate without side effects.[24]

Surgical therapies

When the lesions are stable and vitiligo is refractory to medical treatments, we can consider surgical therapies to induce repigmentation quite effectively, although the long-repigmentation has been poorly assessed.

The surgical techniques can be generally divided into three types.

1. Tissue grafts, in which the whole of epidermis/dermis is transplanted and include suction blister graft, full thickness punch graft (minigraft) and follicular unit grafting.

2. Cellular grafts, which transplant particular cells, including non-cultured epidermal suspension, cultured epidermal cellular graft, cultured melanocyte transplantation and non-cultured hair follicle outer root sheath suspension.

3. Non-grafting surgical techniques such as therapeutic wounding, excision and primary closure and micropigmentation by using a tattoo pen.[39,67]

Conclusions

Vitiligo is a disfiguring disorder with an important effect on the self-esteem and social life of patients; its management is challenging and a trusting relationship between the doctor and the patient is crucial. To date combinations of several treatments appear to be more effective in halting disease progression and obtaining repigmentation than monotherapies. In the current literature there are only a few data about the recurrence rate of different treatments, thus more studies with larger cohorts of patients and, above all, longer follow-up periods are required to substantiate any findings from the current research available.

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