Journal of Pigmentary Disorders
ISSN: 2376-0427

Soura and Katsambas, Pigmentary Disorders 2015, 2:10
DOI: 10.4172/2376-0427.1000213

Review Open Access

Vitiligo, Melanoma Associated Hypopigmentation and Melanoma Incidence and Prognosis: Is There An Association?

Soura E* and Katsambas A

1st Department of Dermatology, University clinic, "Andreas Sygros" Hospital, Athens, Greece

***Corresponding author:** Efthymia Soura, Andreas Sygros Hospital, 5, Dragoumi str, 16121, Athens, Greece, Tel: 0030 6977459330; Fax: 0030 2107258476; E-mail: anonaki@hotmail.com

Rec Date: July 21, 2015; **Acc Date**: September 15, 2015; **Pub Date**: September 20, 2015

Abstract

Malignant melanoma is considered as the most lethal of all skin cancers. However, it is also one of the most immunogenic, characterized by specific antigen presentation and dense lymphocytic infiltration. Many studies concerning melanoma have reported the concurrent presence of vitiligo or Melanoma Associated Hypopigmentation (MAH). This type of vitiligo can appear before or after MM diagnosis, or in tandem with treatment with immunotherapeutic drugs and has been associated with an improved prognosis and/or better response to immunotherapy treatments. This may be attributed to the fact that activated T cells against antigens found on malignant melanocytes can also recognize normal melanocytes and destroy them. On the other side, very limited data exist on whether classic vitiligo can offer protection against or is associated with a decreased incidence of MM. However, MAH represents an example of a strong link between tumor immunity and autoimmune responses. This unique characteristic may be of use as a biomarker in melanoma patients, allowing prediction of MM prognosis or response to specific treatment regimens. Up to this point only a few studies report patient data regarding classic vitiligo and MM. In this paper, the autoimmune hypothesis in the pathogenesis of vitiligo and MAH are discussed, focusing on similarities, differences and known autoantigens. In addition, the results of studies regarding MM and vitiligo or MAH are also summarized.

Keywords: Vitiligo; Melanoma associated hypopigmentation; Melanoma immunotherapies; Melanoma prognosis

Introduction

Vitiligo is an acquired disorder of skin pigmentation. It is characterized by the presence of circumscribed depigmented macules and patches, appearing due to gradual loss of melanocyte function [1]. On the other hand, Melanoma Associated Hypopigmentation (MAH) is a skin depigmentation whose appearance can precede, coincide or follow Malignant Melanoma (MM) diagnosis or, in some instances, can be associated with immunotherapeutic agent treatments [2]. Both conditions are grouped under the category of leukodermas. While MAH is considered to be the result of a strong immune response against specific melanocyte differentiation antigens in melanoma cells [3], the exact pathogenetic mechanism behind vitiligo has not yet been clarified. However, one of the most prominent theories in vitiligo pathogenesis, supports the idea of melanocyte destruction via autoimmune pathways [1]. During recent years, a number of studies and case reports have reported an association between vitiligo and a decreased incidence of melanoma. Some studies also imply that the presence, or appearance, of vitiligo may be associated with a better prognosis for MM patients. This hypothesis is mainly based on the fact that a stronger immune response against melanocytes could yield a protective effect or lead to better treatment results for MM patients. However, one might argue that many patients with vitiligo avoid sun exposure due to the cosmetic reasons, and that this behavior alone could offer protection from skin cancer. When the fact that phototherapy is one of the main treatment options for vitiligo is taken under consideration, the clinical question on how to advise patients regarding sun exposure patterns arises. Another consideration is whether the presence of MAH or vitiligo can be used as a clinical marker for melanoma prognosis or lead to more specific treatment choices.

Vitiligo, MAH and Autoimmunity

According to the autoimmune theory in the pathogenesis of vitiligo, both humoral and cellular autoimmunity play a key role in the appearance of the condition. This hypothesis have been widely accepted and has been supported by several epidemiological, clinical, and laboratory studies [4]. However, it must be mentioned that many different processes, including oxidative stress damage, autotoxicity and neurohumoral factors, could interact in a complicated way to finally lead to vitiligo development [1]. The autoimmune hypothesis is further supported by the fact that patients receiving bone marrow transplants or lymphocyte infusions for the treatment of leukemia, or lymphoma, from donors with vitiligo, were reported to develop new-onset vitiligo as well [4-6]. A number of circulating autoantibodies, belonging mainly to the G class immunoglobulins, have been detected in vitiligo patients [7]. Major melanocytic antigens are considered to include tyrosinase, tyrosinase related protein-1 (TRP-1), TRP-2, gp100 (Pmel17), SOX 9, SOX 10, MART-1 and the type 1 membrane receptor for melanin-concentrating hormone (MCH-R1) among others [8-12]. Cellular immunity plays an important role in vitiligo pathogenesis. The perilesional skin in vitiligo patients exhibits an increased CD8+/CD4+ T cell ratio [13]. This could be the result of an impairment of Treg cell number and function commonly observed in vitiligo patients, which allows for proliferation of CD8+ T cells and secretion of their corresponding cytokines [14-16]. These CD8+ T cells show specificity for antigens such as MART-1, gp100 and tyrosinase and some authors suggest that their activity correlates directly with disease severity

[1,17]. Finally, recent findings advocate a pathogenetic role for specific IL-17 secreting subsets of Th17 cells in vitiligo [4].

Unlike vitiligo, the pathogenetic mechanism of MAH is clearly autoimmune mediated. This autoimmunity is both antibody and T cell mediated [18]. Melanoma is considered to be an extremely immunogenic tumor, able to express a number of antigens, including tyrosinase, TRP-1, TRP-2, gp100 and MART-1 [19]. These, as previously mentioned, are known autoantigens in vitiligo. It must be noted, though, that data concerning antibody-mediated vitiligo in melanoma patients have been limited [20]. Cell mediated autoimmunity seems to play a more important role in MM patients with MAH. MMs are infiltrated by a higher number of lymphocytes compared to other types of tumors [21]. Activated cytotoxic T cells and autoantibodies, able to recognize melanoma cells, can react with antigens normally expressed by naïve melanocytes and therefore lead to the appearance of various types of melanoma associated leukodermas, including Sutton nevi and MAH [21]. CD8+ T cells from both tumors and peripheral blood of melanoma patients have been shown to kill both normal melanocytes and melanoma cells in ex vivo studies [22,23], while identical T cell clones have been found in both tumor and surrounding depigmented lesions in MM patients [24]. CD4+ T cell mediated immunity seems to play a less important role in MAH pathogenesis. However, some recent studies have demonstrated increased levels of IL-17 in both the serum and tissue of vitiligo patients [20].

A number of authors have attempted to describe the immunological profile of patients with vitiligo and MAH. Recent studies have demonstrated that depigmented skin of patients with MAH or vitiligo exhibits absent or strongly reduced MART-1 and gp100 positive melanocytes [3,25]. Furthermore, Teulings et al. have reported the presence of T cells against MART-1, gp100 and tyrosinase in both patients with MAH and vitiligo. However, the levels of T cells were different between MAH and vitiligo patients and were dependent on disease activity for vitiligo patients [3]. In addition, in this study autoantibodies to gp100 and tyrosinase were found in both vitiligo and MAH patients, while MART-1 autoantibodies were found only in MAH patients [3]. Waterman et al. also report a lack of MART-1 autoantibodies in vitiligo patients, suggesting that MART-1 can activate only cellular immunity [26]. A number of other studies provide data that contradict or corroborate these findings [27-29]. Very few published data exist on the levels of MART-1 autoantibodies in patients with melanoma receiving immunotherapy, or their correlation with melanoma associated hyperpigmentation in those patients. Teulings et al. report MART-1 positivity in 4 patients with MAH in the context of metastatic melanoma [3]; however more studies are needed in order to clarify the utility of this antigen in MM prognosis.

Vitiligo, MAH and Malignant melanoma

It is estimated that 2-16% of patients with MM develop MAH [25]; while some authors suggest that this could be higher for patients receiving immunotherapy [30]. However, in a recent metanalysis by Teulings et al. which included data from studies with MM patients treated with various types of immunotherapies, MAH prevalence was found to be 3.4% (95% CI, 2.5% to 4.5%) [31]. On the other hand, the true incidence of vitiligo in MM patients is not clearly defined. This could be due to different criteria of reporting between studies [32], the fact that most data come from small case series/ reports with a small sample of patients [30,33]or, in general, due to clinical difficulties in distinguishing from MAH appearing as a precursor symptom for MM. The features of these two entities, as reported, by various authors are summarized in Table 1.

Characteristics	Vitiligo	Melanoma Associated Hypopigmentation
Age (years)	27.6 ± 16,5	56.4 ± 10.8
Gender	Females (@70%)	No distinction (1:1)
Distribution	bilateral symmetric pattern (vitiligo vulgaris)	· Similar to vitiligo vulgaris
		· Pericicatricial
		· Rarely: unilateral asymmetric or focal hypopigmentation
Autoimmune diseases	· Thyroid disease	Similar to vitiligo patients
	· Various autoimmune disorders present	
	· Positive family history for vitiligo	
Acquired leukodermas (hypopigmented scars, Sutton nevi)	Rarely	More common than in vitiligo patients
Autoantibodies	· Tyrosinase +	· Tyrosinase +
	· gp100 +	· gp100 +
	· MART-1 - (?)	· MART-1 +

Table 1: Characteristics of vitiligo and MAH [23,27,34].

During the last few years, a small number of studies reported a decreased incidence of MM in vitiligo patients. Teulings et al. reported a threefold decreased probability (adjusted OR 0,32,95% CI 0,12-0,88) for the development MM in 1307 patients with vitiligo compared to controls [34]. Similar results were also reported by Paradisi et al. in a study that included 10,040 patients with vitiligo [35]. More specifically, the crude RR for melanoma was found to be 0.24 (95% CI 0,13-0,45) in patients with vitiligo when compared with the control group (occurrence 1,1‰, 95% CI 0,5‰-2,0‰ in patients with vitiligo vs. 4.5‰, 95% CI 3.8‰- 5.4‰ in controls) [35]. Interestingly, this result was not completely applicable for patients that underwent phototherapy treatments in the past. As a matter of fact, these patients exhibited a sevenfold risk of MM compared to that of patients who did not undergo phototherapy (6.0‰ vs 0.8‰) [35]. These results were contradicted by the Teulings study where phototherapy was not found to be a risk factor in patients with vitiligo [34]. In addition, it was reported that all MMs had appeared in non-vitiligo skin. However, total number of nevi (>100) and painful sunburn during childhood were positively associated with a higher risk of MM [34]. Although the place of phototherapy as a predisposing factor for MM in vitiligo patients has not yet been clarified, the overall results of these studies are rather surprising. One would expect that vitiligeneous patches should be more susceptible to carcinogenesis due to the lack of protective melanocytes. Interestingly, in a recent study by Jin et al. a mutation in TYR gene (tyrosinase) that may indicate a mutually exclusive relationship between susceptibility to vitiligo and susceptibility to MM was revealed [36]. At this point there are very

limited data on vitiligo and melanoma prognosis and response to therapy.

MAH is considered a distinct nosological entity from vitiligo and is directly associated with the presence of malignant melanoma or administration of immunotherapy for its treatment. Schallreuter et al. have suggested that patients with MM have a 7 to 10-fold higher possibility of developing vitiligo compared to controls [37]. In addition, it was reported that ≅50% of cases developed the condition before MM diagnosis. In this study the prevalence of vitiligo in MM patients was 3.7% [37]. In a more recent study by Quaglino et al. it was reported that 20.5% of vitiligo patients had presented with vitiligo before the MM diagnosis (age of onset 2-45 years previous to diagnosis), while the remaining 79.5% developed vitiligo after melanoma excision (median time 3,4 years, range 2 months-20 years) [32]. These two groups of patients showed demographic and clinical differences. Patients with vitiligo appearing previous to MM diagnosis were younger (median age 38 years) and presented with a more generalized distribution of vitiligo compared to those with vitiligo appearing after MM diagnosis [32]. Similar results were reported by other authors [25,38]. In addition, the prognosis of MM may be more favorable for those patients. Bystryn et al. have reported an actual average five-year survival rate for patients with MM and hypopigmentation of 86.3% compared to 74.8% of that observed in MM patients without hypopigmentation [39]. In the Quaglino study the survival data were stratified according to melanoma staging. No statistically important differences were observed in the 5-year survival rates for stage I and II MMs in patients with vitiligo and in patients without vitiligo (95.6% vs 95.4% and 74.4% vs 68.8%, respectively). However, an important difference was observed for stage III MMs (5-year survival 65% in vitiligo patients vs 42.5% in patients without vitiligo; P=0.03). In addition, the distant metastasis free survival for those patients was 52.4% compared to 21.5% in patients without vitiligo [32]. These results are intriguing, since they support the hypothesis of a possible biological significance for vitiligo developing in melanoma patients.

A number of studies that included MM patients receiving immunotherapy treatments have reported the appearance of MAH in specific subsets of those patients. Quaglino et al. reported that about 2.8% of MM patients will develop MAH regardless of treatment [32]. Interestingly, a small number of studies have demonstrated a possible link of immunotherapy associated MAH with a more favorable MM prognosis [32,38,40-42]. For instance, Phan et al. reported that out of 14 MM patients treated with anti-CTLA-4 antibodies, the 3 patients that presented with objective responses had developed autoimmunity, including vitiligo (2 patients) [43]. Similar results were reported by Boasberg et al. [44] It was shown that metastatic MM patients who developed vitiligo during maintenance biotherapy (21 patients, 43%) exhibited an improved median overall survival (18.2 months, 95% CI, 12.3-N/A) compared to non-vitiligo patients (8.5 months, 95%CI <6.7–12.7) [44]. The point repeated in those studies is that heightened autoimmune responses, that could also be expressed as vitiligo appearance, in MM patients receiving immunotherapy may be associated with a more favorable prognosis. In a study by Gogas et al. 200 patients with high risk melanomas receiving interferon therapy were investigated [45]. Antibodies or clinical evidence of autoimmunity was observed in 26% of patients, including 11 (6%) patients with new onset vitiligo (MAH). After a median follow up of 45.6 months, only 7% of patients with autoimmune manifestations experienced disease recurrence, compared to 73% of the patients with no autoimmune manifestations. Overall, the development of autoimmunity was associated in this study with both improved relapse-free survival (HR, 0.12; 95% CI, 0.05-0.25; P<0.001) and longer overall survival intervals (HR, 0.02; 95% CI, <0.01-0.15; P<0.001) [45]. Teulings et al. authored a meta-analysis in an effort to prove whether such observations can be extrapolated to include all patients receiving immunotherapies [31]. A total of 137 studies were included in the meta-analysis. Out of those, only 27 studies included patient data in vitiligo. A higher incidence of MAH observed in patients receiving therapy with adoptive transfer of cytotoxic T-lymphocytes (6.3%), although the pooled cumulative incidence of vitiligo was found to be 3.4% (5,737 patients with stage III or IV melanoma on immunotherapy) [31]. Regarding progression free survival and overall survival, the results of the meta-analysis were rather impressive since progression-free survival (HR, 0.51; 95% CI, 0.32–0.82; P<0.005) and overall survival values (HR, 0.25; 95% CI: 0.10-0.61; P<0.003) indicated that vitiligo patients exhibit a two and four times less risk of disease progression and death, respectively, compared to those without vitiligo development [31].

Conclusion

Autoimmunity has not been shown to be associated with a decreased incidence or prognosis of MM [46]. Vitiligo and MAH, however, present with a very specific autoimmune profile. Both conditions have been associated with the presence of autoantibodies directed against antigen targets also found on malignant melanocytes. At this point there are no clear data that can infer whether vitiligo can offer protection from MM. Therefore patients should not be encouraged to follow reckless sun seeking behaviors. In addition, when phototherapy is selected for vitiligo treatment, patients should be followed up for skin cancer in the same way as all other patients receiving the same treatment regimen. However, vitiligo appearance in patients with MM or patients receiving immunotherapy has been clearly linked with an improved prognosis. It must be noted that although there is a multitude of studies regarding the use of immunotherapies for treating MM, only a few report patient data regarding vitiligo or MAH. Although there are indeed only limited data on MAH and patient prognosis or response to treatment, it has become evident that there is a need to further investigate this association. In addition, at this point there are no precise clinical criteria for the distinction between MAH and vitiligo. This can be considered as a limitation when describing study results. In a world where personalized medicine becomes more and more tangible, the definition of a patient endotype that would allow for appropriate treatment choice is important. Patients that present with vitiligo or MAH may harbor a distinct genetic profile that would allow them to produce a more optimal response against MM. This could mean that this inherent ability of the immune system could work synergistically with an immunotherapy treatment, allowing for optimal treatment responses, or could indeed offer protection from melanocyte malignant transformation in a more basic level.

References

1. Alikhan A, Felsten LM, Daly M, Petronic-Rosic V (2011) Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol 65: 473-491.
2. Gathings R, Lewallen R, Yosipovitch G (2015) Immunotherapy-induced leukoderma from treatment of melanoma with IL-2: a case report and a review of the literature. Acta Derm Venereol 95: 197-200.
3. Teulings HE, Willemsen KJ, Glykofridis I, Krebbers G, Komen L, et al. (2014) The antibody response against MART-1 differs in patients with melanoma-associated leucoderma and vitiligo. Pigment Cell Melanoma Res 27: 1086-1096.

4. Colucci R, Dragoni F, Moretti S (2015) Oxidative stress and immune system in vitiligo and thyroid diseases. Oxid Med Cell Longev 2015: 631927.
5. Alajlan A, Alfadley A, Pedersen KT (2002) Transfer of vitiligo after allogeneic bone marrow transplantation. J Am Acad Dermatol 46: 606-610.
6. Au WY, Yeung CK, Chan HH, Lie AK (2001) Generalized vitiligo after lymphocyte infusion for relapsed leukaemia. Br J Dermatol 145: 1015-1017.
7. Uda H, Takei M, Mishima Y (1984) Immunopathology of vitiligo vulgaris, Sutton's leukoderma and melanoma-associated vitiligo in relation to steroid effects. II. The IgG and C3 deposits in the skin. J Cutan Pathol 11: 114-124.
8. Okamoto T, Irie RF, Fujii S, Huang SK, Nizze AJ, et al. (1998) Anti-tyrosinase-related protein-2 immune response in vitiligo patients and melanoma patients receiving active-specific immunotherapy. J Invest Dermatol 111: 1034-1039.
9. Kemp EH, Gawkrodger DJ, Watson PF, Weetman AP (1998) Autoantibodies to human melanocyte-specific protein pmel17 in the sera of vitiligo patients: a sensitive and quantitative radioimmunoassay (RIA). Clin Exp Immunol 114: 333-338.
10. Hedstrand H, Ekwall O, Olsson MJ, Landgren E, Kemp EH, et al. (2001) The transcription factors SOX9 and SOX10 are vitiligo autoantigens in autoimmune polyendocrine syndrome type I. J Biol Chem 276: 35390-35395.
11. Kemp EH, Waterman EA, Hawes BE, O'Neill K, Gottumukkala RV, et al. (2002) The melanin-concentrating hormone receptor 1, a novel target of autoantibody responses in vitiligo. J Clin Invest 109: 923-930.
12. Mandelcorn-Monson RL, Shear NH, Yau E, Sambhara S, Barber BH, et al. (2003) Cytotoxic T lymphocyte reactivity to gp100, MelanA/MART-1, and tyrosinase, in HLA-A2-positive vitiligo patients. J Invest Dermatol 121: 550-556.
13. Le Poole IC, van den Wijngaard RM, Westerhof W, Das PK (1996) Presence of T cells and macrophages in inflammatory vitiligo skin parallels melanocyte disappearance. Am J Pathol 148: 1219-1228.
14. Dwivedi M, Kemp EH, Laddha NC, Mansuri MS, Weetman AP, et al. (2015) Regulatory T cells in vitiligo: Implications for pathogenesis and therapeutics. Autoimmun Rev 14: 49-56.
15. Lili Y, Yi W, Ji Y, Yue S, Weimin S, et al. (2012) Global activation of CD8+ cytotoxic T lymphocytes correlates with an impairment in regulatory T cells in patients with generalized vitiligo. PLoS One 7: e37513.
16. Dwivedi M1, Laddha NC, Arora P, Marfatia YS, Begum R (2013) Decreased regulatory T-cells and CD4(+) /CD8(+) ratio correlate with disease onset and progression in patients with generalized vitiligo. Pigment Cell Melanoma Res 26: 586-591.
17. Palermo B, Campanelli R, Garbelli S, Mantovani S, Lantelme E, et al. (2001) Specific cytotoxic T lymphocyte responses against Melan-A/MART1, tyrosinase and gp100 in vitiligo by the use of major histocompatibility complex/peptide tetramers: the role of cellular immunity in the etiopathogenesis of vitiligo. J Invest Dermatol 117: 326-332.
18. Michelsen D (2010) The Double Strike Hypothesis of the vitiligo pathomechanism: new approaches to vitiligo and melanoma. Med Hypotheses 74: 67-70.
19. Barrow C, Browning J, MacGregor D, Davis ID, Sturrock S, et al. (2006) Tumor antigen expression in melanoma varies according to antigen and stage. Clin Cancer Res 12: 764-771.
20. Byrne KT, Turk MJ (2011) New perspectives on the role of vitiligo in immune responses to melanoma. Oncotarget 2: 684-694.
21. Naveh HP, Rao UN, Butterfield LH (2013) Melanoma-associated leukoderma - immunology in black and white? Pigment Cell Melanoma Res 26: 796-804.
22. Oyarbide-Valencia K, van den Boorn JG, Denman CJ, Li M, Carlson JM, et al. (2006) Therapeutic implications of autoimmune vitiligo T cells. Autoimmun Rev 5: 486-492.
23. Anichini A, Maccalli C, Mortarini R, Salvi S, Mazzocchi A, et al. (1993) Melanoma cells and normal melanocytes share antigens recognized by HLA-A2-restricted cytotoxic T cell clones from melanoma patients. J Exp Med 177: 989-998.
24. Becker JC, Guldberg P, Zeuthen J, Bröcker EB, Straten PT (1999) Accumulation of identical T cells in melanoma and vitiligo-like leukoderma. J Invest Dermatol 113: 1033-1038.
25. Hartmann A, Bedenk C, Keikavoussi P, Becker JC, Hamm H, et al. (2008) Vitiligo and melanoma-associated hypopigmentation (MAH): shared and discriminative features. J Dtsch Dermatol Ges 6: 1053-1059.
26. Waterman EA, Kemp EH, Gawkrodger DJ, Watson PF, Weetman AP (2002) Autoantibodies in vitiligo patients are not directed to the melanocyte differentiation antigen MelanA/MART1. Clin Exp Immunol 129: 527-532.
27. Dordic M, Matic IZ, Filipovic-Ljeskovic I, Dzodic R, Sasic M, et al. (2012) Immunity to melanin and to tyrosinase in melanoma patients, and in people with vitiligo. BMC Complement Altern Med 12: 109.
28. Fishman P, Merimski O, Baharav E, Shoenfeld Y (1997) Autoantibodies to tyrosinase: the bridge between melanoma and vitiligo. Cancer 79: 1461-1464.
29. Merimsky O, Shoenfeld Y, Baharav E, Altomonte M, Chaitchik S, et al. (1996) Melanoma-associated hypopigmentation: where are the antibodies? Am J Clin Oncol 19: 613-618.
30. Rosenberg SA, White DE (1996) Vitiligo in patients with melanoma: normal tissue antigens can be targets for cancer immunotherapy. J Immunother Emphasis Tumor Immunol 19: 81-84.
31. Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, et al. (2015) Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol 33: 773-781.
32. Quaglino P, Marenco F, Osella-Abate S, Cappello N, Ortoncelli M, et al. (2010) Vitiligo is an independent favourable prognostic factor in stage III and IV metastatic melanoma patients: results from a single-institution hospital-based observational cohort study. Ann Oncol 21: 409-414.
33. Gül U, Kiliç A, Tulunay O, Kaygusuz G (2007) Vitiligo associated with malignant melanoma and lupus erythematosus. J Dermatol 34: 142-145.
34. Teulings HE, Overkamp M, Ceylan E, Nieuweboer-Krobotova L, Bos JD, et al. (2013) Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. Br J Dermatol 168: 162-171.
35. Paradisi A, Tabolli S, Didona B, Sobrino L, Russo N, et al. (2014) Markedly reduced incidence of melanoma and nonmelanoma skin cancer in a nonconcurrent cohort of 10,040 patients with vitiligo. J Am Acad Dermatol 71: 1110-1116.
36. Jin Y, Birlea SA, Fain PR, Gowan K, Riccardi SL, et al. (2010) Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. N Engl J Med 362: 1686-1697.
37. Schallreuter KU, Levenig C, Berger J (1991) Vitiligo and cutaneous melanoma. A case study. Dermatologica 183: 239-245.
38. Nordlund JJ, Kirkwood JM, Forget BM, Milton G, Albert DM, et al. (1983) Vitiligo in patients with metastatic melanoma: a good prognostic sign. J Am Acad Dermatol 9: 689-696.
39. Bystryn JC, Rigel D, Friedman RJ, Kopf A (1987) Prognostic significance of hypopigmentation in malignant melanoma. Arch Dermatol 123: 1053-1055.
40. Scheibenbogen C, Hunstein W, Keilholz U (1994) Vitiligo-like lesions following immunotherapy with IFN alpha and IL-2 in melanoma patients. Eur J Cancer 30A: 1209-1211.
41. Dudley ME, Wunderlich JR, Robbins PF, Yang JC, Hwu P, et al. (2002) Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science 298: 850-854.
42. Luiten RM, Kueter EW, Mooi W, Gallee MP, Rankin EM, et al. (2005) Immunogenicity, including vitiligo, and feasibility of vaccination with autologous GM-CSF-transduced tumor cells in metastatic melanoma patients. J Clin Oncol 23: 8978-8991.
43. Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, et al. (2003) Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci U S A 100: 8372-8377.

44. Boasberg PD, Hoon DS, Piro LD, Martin MA, Fujimoto A, et al. (2006) Enhanced survival associated with vitiligo expression during maintenance biotherapy for metastatic melanoma. J Invest Dermatol. 126: 2658-2663.

45. Gogas H1, Ioannovich J, Dafni U, Stavropoulou-Giokas C, Frangia K, et al. (2006) Prognostic significance of autoimmunity during treatment of melanoma with interferon. N Engl J Med 354: 709-718.

46. Kaae J, Wohlfahrt J, Boyd HA, Wulf HC, Biggar RJ, et al. (2007) The impact of autoimmune diseases on the incidence and prognosis of cutaneous malignant melanoma. Cancer Epidemiol Biomarkers Prev 16: 1840-1844.