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COMMENTARY

Vitiligo: 30 years to put together the puzzle pieces and to give rise to a new era of therapeutic options

Back to the 90s, most of the articles on vitiligo started with the same sentence: 'The pathophysiology of vitiligo remains largely unknown and there is no effective treatment'. For the 1–2% of people suffering from vitiligo in the world, generations of patients had to hear from their physicians that vitiligo was a cosmetic disease, probably due to stress, without any therapeutic solution, and that they must strictly protect their skin from the sun to avoid skin cancers! For where we stand today, we can clearly see the outstanding achievements that have been done by researchers and clinicians during these past three decades. Underlying the main achievements in a commentary article with no more than 10 references is an impossible task leading to subjective choices that could never bring justice to all the work done during the past 30 years.

Fighting preconceive ideas

One of the key advances for the patients was the demonstration of the impact of vitiligo on the quality of life on many affected individuals. In 1996, a large survey demonstrated that patients with vitiligo suffer from significant distress.[1] Since then, many studies have confirmed the profound impact that vitiligo can have on the social, sexual and professional life. These data emphasized the crucial need of effective approaches to treat patients who suffer from their vitiligo.

The decreased risk of skin cancers in vitiligo patients compared to the general population is known for <10 years.[2] These data, since confirmed by other groups, sound now quite logical, at least for the melanoma risk, when we know the anti-melanocytic immune response occurring in vitiligo. This demonstration is of great importance as without sun, or more generally ultraviolet (UV) exposure, the possibility of repigmentation is critically impaired. Unfortunately, many physicians are still not aware about this important fact and continue recommending a strict photoprotection to their patients, thus preventing them to repigment.

The key events of the pathophysiology revealed

Several hypotheses were raised for explaining the pathophysiology of vitiligo. Many groups discovered progressively the pieces of this complex puzzle. The role of the genetic background with allelic variations predisposing to the occurrence of vitiligo was revealed by large genome wide association studies.[3] These studies found an association with melanocytic genes but mostly demonstrated the involvement of genes involved in innate and adaptative immunity. Although the first evidence suggesting the role of immunity in vitiligo was reported in the 70s, the development of vitiligo mouse models allowed significant advances. The demonstration of the Th1 response with the activation of the interferon gamma pathway fostered the development of JAK inhibitors that are now clinically tested orally and topically for vitiligo.[4] The impact of the innate immunity in the early stages of vitiligo development is also now clearly demonstrated. It is the link between external or internal stressors and the activation of the adaptative immunity against melanocytes. As observed in many autoimmune disorders, a decrease in regulatory T cells has been also reported in vitiligo. Importantly, memory T cells accumulate in vitiligo lesions and probably explain the high rate of recurrence in the previously affected areas.[5] Since the early report of epidermal defects in normal appearing skin from vitiligo patients in the 80s, several studies have shown alteration in melanocytes (including in the antioxidant machinery), but also in keratinocytes and fibroblasts. That these defects pre-exist or are secondary to the immune response, remains a matter of debate. Lastly, a decrease in the WNT pathway, that is critical for melanocyte stem cell differentiation, has been reported in vitiligo skin.[6] These defects probably explain the difficulties for repigmenting areas such as hands and feet and offer new perspectives to enhance repigmentation without using UV.

The first steps that allowed improving the care of vitiligo patients

Pioneers proposed grafts for depigmented vitiligo lesions in the 50s. During the past three decades, improvement in techniques have been reported. However, the main advances came from the medical treatment of vitiligo. Topical calcineurin inhibitors were found to be as effective as topical steroids but offer better long-term tolerance in sensitive areas. New sources of UVB, such as excimer lasers and lamps, demonstrated their efficacy, especially for localized forms, but it is clearly the combination approaches associating UV sources with topical calcineurin inhibitors or topical steroids that brought significant better rates of repigmentation.[7] Similarly, combination of narrowband UVB and oral mini pulses of steroids was shown to be an effective option for active forms of vitiligo.[8] The first demonstration of the efficacy of a

Table 1 Upcoming potential options for treating vitiligo

	Targets	Compounds	Clinical indications
1st generation	CD4+ & CD8+ T cells	Topical JAK inhibitors (JAK1/2)	Repigmenting localized forms
	CD4+ & CD8+ T cells and NK	Oral JAK inhibitors (JAK1/2; JAK3/TEC)	Repigmenting widespread and/or active forms
	Dendritic cells	Oral JAK inhibitors (JAK1/TYK2)	Early stages / preventing extension
2nd generation	Dendritic cells	Anti-aBCDA2 antibodies	Early stages / preventing extension
	DAMPs	Topical mutant HSP70 gene-gun delivery	Early stages / preventing extension
	DAMPs	New generation of oral or topical antioxidants	Promoting repigmentation / early stages / preventing extension
	PAMPs / Microbiome	Oral or topical probiotics or postbiotics	Early stages / preventing extension
	CD8+ T cells and NK	Anti-NKG2D antibodies	Repigmenting widespread and/or active forms
	TREGS	Low dose of new generation of IL-2	Repigmenting widespread and/or active forms
	TREGS	Anti-CD86-IL-10 antibodies	Repigmenting widespread and/or active forms
	TREGS	Topical CCL22 gene-gun delivery	Repigmenting localized forms
	CD8+ T cells and T resident memory cells	Anti-IL-15 antibodies	Promoting repigmentation / preventing relapses
	Melanocyte detachment	MMP-9 inhibitors	Promoting repigmentation / early stages / preventing extension
	Melanocyte apoptosis	Anti-CXCR3B blocking antibodies	Promoting repigmentation / early stages / preventing extension
	Melanocyte stem cells	WNT agonists / GSK3b inhibitors	Repigmenting resistant areas

NK, Natural Killer; HSP70, Heat shock protein 70; DAMPs, Damage-associated molecular patterns; PAMPs, Pathogen-associated molecular patterns; TREGS, T regulatory cells; MMP9, Matrix metalloproteinase 9.

maintenance treatment using twice weekly applications of 0.1% topical tacrolimus significantly reduces the risk of relapses after achieving repigmentation.[9]

Towards a new era of treatments for vitiligo

Despite those therapeutic advances, the care of vitiligo patients remains challenging. No repigmenting treatment is still approved by agencies. The best repigmentation rates are obtained on the face, but even in this location, about one third of patients do not achieve complete or almost complete repigmentation despite 6–24 months of combination treatment. Results are more disappointing on the rest of the body, and some areas such as the extremities of the hands and feet are almost impossible to repigment. In those areas, topical treatment that could allow inducing the differentiation of melanoblasts to pigmented melanocytes is mandatory. Widespread and active forms of vitiligos require effective and well-tolerated systemic treatments. Approaches to halt disease progression from the first signs of the disease, or to prevent relapses after achieving repigmentation, would be of critical interest for the patients.

Thanks to the key advances in the pathophysiology, those new approaches are developed (see Table 1). The most advanced ones are topical JAK inhibitors that already demonstrated their efficacy in a phase 2 trial.[10] Oral JAK inhibitors are currently tested for widespread or active vitiligos. These are only the first wave of treatments. Several other compounds targeting many types of potential targets offer encouraging perspectives. Hopefully, they should complete the therapeutic arsenal for vitiligo patients in the coming years.

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