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VITILIGO - IMMUNOPATHOGENESIS AND INVASIVE CORRECTION METHODS IN CLINICAL PRACTICE

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Abstract
Vitiligo is a chronic autoimmune depigmentation disorder affecting 0.5-2% of the global population. Destruction of epidermal melanocytes is driven primarily by CD8 cytotoxic T lymphocytes through IFN-γ-CXCL9/CXCL10-CXCR3 signaling axis and JAK/STAT pathway activation. When conservative therapies fail, invasive surgical correction - including punch grafting, suction blister grafting, split-thickness skin grafting, and non-cultured melanocyte-keratinocyte transplantation - offers clinically meaningful repigmentation. This review synthesizes current immunopathogenetic data with quantitative outcomes of major invasive techniques.

Keywords: Melanocyte, depigmentation, immunopathogenesis, autoreactive lymphocytes, JAK/STAT pathway, IFN-γ, CXCL10, punch grafting, melanocyte-keratinocyte transplantation, suction blister graft, repigmentation, VASI score, Koebner phenomenon, oxidative stress, segmental vitiligo.

Introduction

Vitiligo ranks among the most psychologically disabling dermatoses. It presents as sharply demarcated achromic macules of variable size on skin and mucous membranes, with a worldwide prevalence consistently estimated at 0.5-2% irrespective of sex or ethnicity. Approximately 70% of cases manifest before the age of 30, and roughly 25% arise in children under ten years. The condition follows a chronic, unpredictable course: periods of apparent stability alternate with episodes of rapid spreading, which makes treatment planning difficult. Despite decades of research, no single modality achieves sustained, complete repigmentation across all patients. Conservative therapies - topical corticosteroids, calcineurin inhibitors, narrowband ultraviolet B phototherapy - stabilize or partially reverse pigment loss in many cases, yet a substantial subset remains refractory, necessitating surgical or other invasive interventions. Understanding the cellular and molecular mechanisms underlying melanocyte destruction is therefore not merely an academic exercise but a prerequisite for selecting the most rational corrective strategy for individual patients.

Literature review

The autoimmune basis of vitiligo has been established through convergent lines of evidence over the past three decades. Speeckaert et al. (2024) demonstrated that both segmental and non-segmental vitiligo share a core inflammatory mechanism in which melanocyte-specific CD8 T cells drive

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depigmentation via IFN-γ and downstream JAK/STAT signaling. Liu et al. (2024) elaborated the IFN-γ-CXCL9/CXCL10-CXCR3 axis as a self-amplifying loop responsible for progressive lesion expansion. Albelowi et al. (2024) reviewed genetic predisposition, oxidative stress, and environmental triggers as upstream initiators of this immune cascade. On the interventional side, a systematic review and meta-analysis by Jin et al. (2021) encompassing 117 studies and 8,776 patients provided the most comprehensive quantitative synthesis of surgical outcomes for stable vitiligo to date. Iwanowski et al. (2023) reviewed emerging pharmacological targets, particularly JAK inhibitors, as adjuncts to surgical repigmentation. Collectively, the literature supports a two-stage model: immune-mediated melanocyte exhaustion followed by a structural melanocyte deficit that conservative therapies alone cannot adequately address.

Methodology

Study design and data sources. This narrative-analytical review was conducted according to a structured literature search strategy. Databases queried included PubMed/MEDLINE, Scopus, Web of Science, and the Russian Scientific Electronic Library (eLIBRARY.ru) for the period 2019-2024, supplemented by seminal earlier works published between 1999 and 2018 where quantitative clinical data were unavailable in more recent literature. Search terms included: "vitiligo pathogenesis," "melanocyte destruction," "CD8+ T cells vitiligo," "IFN-gamma vitiligo," "JAK STAT vitiligo," "punch grafting vitiligo outcomes," "melanocyte-keratinocyte transplantation," "suction blister grafting," "split-thickness skin graft vitiligo," and "VASI score." Articles were included if they reported original clinical data with quantifiable repigmentation outcomes, described immunomolecular mechanisms with experimental evidence, or constituted meta-analyses and systematic reviews. Case reports involving fewer than ten patients were excluded, as were studies lacking a defined stability criterion for surgical candidacy. Stability criteria applied across reviewed studies. All surgical studies in this review required patients to meet a minimum disease stability period of at least 12 months with no new lesions and a negative Koebner phenomenon on test grafting. This criterion is fundamental: disease activity after grafting was reported in 94% of patients who achieved poor repigmentation versus only 18% of those with excellent repigmentation outcomes ($p < 0.0005$), confirming that stability is the single most predictive pre-operative variable.

Invasive techniques evaluated. Four primary invasive modalities were analyzed:

Punch grafting (PG). The technique involves harvesting autologous full-thickness skin plugs, typically 1.0-2.0 mm in diameter, from a pigmented donor site - most commonly the gluteal or inner thigh region - and transplanting them into recipient holes of identical diameter prepared within the depigmented patch. In comparative studies, 1.5 mm grafts demonstrated a significantly larger repigmented surface area at six-month follow-up compared with 1.0 mm grafts ($p < 0.001$), though the larger grafts were associated with a higher incidence of side effects. A punch depth of 1.5 mm in superficial configuration is currently recommended for trunk and proximal extremities. Suction blister epidermal grafting (SBEG). Suction blisters are induced at 150-300 mmHg over 1-3 hours on normal donor skin. The blister roof, comprising viable epidermis with intact melanocytes, is harvested and transferred to a recipient site from which the depigmented epidermis has been removed by dermabrasion or CO laser ablation. The technique is particularly suited for cosmetically sensitive areas such as the face and dorsum of the hands because it leaves no visible donor scar.

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Split-thickness skin grafting (STSG). Thin dermal shavings of 0.2-0.3 mm thickness are harvested using a dermatome and applied to dermabrasion-prepared recipient beds. This approach permits coverage of larger surface areas compared with punch or blister techniques but carries a higher risk of surface irregularity and scarring.

Non-cultured melanocyte-keratinocyte transplantation procedure (MKTP). MKTP involves enzymatic disaggregation of a donor epidermal sample with trypsin-EDTA solution, yielding a cell suspension containing approximately 70,000-100,000 melanocytes per cm of donor tissue. This suspension is applied to a recipient site where the epidermis has been removed. The donor-to-recipient area ratio ranges from 1:3 to 1:10, allowing relatively small donor areas to resurface large depigmented zones, up to 500 cm. Outcome measurement. Repigmentation was assessed using the Vitiligo Area Scoring Index (VASI), introduced by Hamzavi et al., which quantifies both lesion extent and degree of repigmentation. Outcomes were classified as: excellent (>90% repigmentation), good (51-90%), moderate (26-50%), and poor (25%). Follow-up periods across included studies ranged from 6 months to 108 months (mean: 43 months; median: 36 months).

Results

Immunopathogenetic findings. The central cellular event in vitiligo is the apoptosis and detachment of basal layer melanocytes mediated by autoreactive CD8 cytotoxic T lymphocytes. These cells, expressing CXCR3 on their surface, are recruited to lesional skin in response to CXCL9 and CXCL10 chemokines produced by keratinocytes following IFN-γ stimulation. IFN-γ, secreted predominantly by skin-homing CD8 T cells, activates the JAK1/2-STAT1 signaling cascade in keratinocytes, which amplifies local CXCL9/CXCL10 production and sustains a positive-feedback inflammatory cycle. Three distinct mechanisms of melanocyte death have been identified: (1) perforin/granzyme-mediated cytolysis by CD8 T cells, (2) Fas-FasL apoptotic signaling, and (3) direct apoptosis induction via CXCR3B - an isoform expressed exclusively on human, but not murine, melanocytes - activated by CXCL10 independently of T cell contact. IFN-γ further disrupts melanocyte attachment by inducing MMP-9-driven cleavage of E-cadherin and suppressing E-cadherin gene expression, thereby loosening intercellular adhesion at the dermal-epidermal junction before frank T cell-mediated destruction occurs. Melanocyte antigens identified as primary targets of autoreactive T cells include MelanA/Mart1, gp100, and tyrosinase.

Surgical outcomes - punch grafting. In the largest prospective dataset of autologous miniature punch grafting, involving 1,000 patients with stable and refractory vitiligo, positive test-graft results were obtained in 880 patients (88%). Among these, 90-100% repigmentation was achieved in 656 patients (74.55%). No spread of pigment was observed in 93 patients (10.57%), and graft depigmentation occurred in 21 patients (2.39%). The most frequent complications were polka-dot appearance (43.98%) and color mismatch (34.32%). Long-term follow-up data from a prospective cohort of 70 patients (61 with vitiligo vulgaris, 9 with segmental vitiligo) undergoing 2 mm punch grafting showed that among segmental vitiligo patients, 7 of 9 lesions (78%) achieved excellent repigmentation at a mean follow-up of 5.2 years. In the vitiligo vulgaris group, results were distributed as follows: excellent 28%, good 23%, fair 23%, and poor 26%. A cobblestone-like surface effect was observed in 19 of 70 patients (27%), which was reduced to acceptable levels when graft diameter was restricted to 1.0-1.2 mm.

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Surgical outcomes - MKTP. The most extensive long-term dataset on MKTP comprised 2,283 patients with follow-up periods ranging from 12 to 108 months. Excellent repigmentation (>90%) was achieved in: 66% of patients with segmental vitiligo, 58.8% of those who received pre-MKTP phototherapy, 63.9% of patients younger than 24 years at the time of surgery, and 75% of patients with lesions located on the perineum and scrotum. Patients with a positive family history of vitiligo responded significantly worse ($\chi = 29.417$, $p < 0.001$), as did those demonstrating a positive Koebner phenomenon ($\chi = 107.397$, $p < 0.001$). A significant positive correlation between the duration of pre-operative disease stability and the percentage of final repigmentation was confirmed ($\chi = 42.053$, $p < 0.001$). Cultured autologous melanocyte transplantation, performed in a separate series, achieved clinical remission (80-100% repigmentation) in 92.3% of patients.

Surgical outcomes - SBEG and STSG. For non-cultured melanocyte transfer techniques overall - including punch grafting, suction blister grafting, split-thickness grafting, and follicular unit extraction - the published success rate ranges from 60% to 80%. Thin STSG combined with adjuvant excimer laser treatment demonstrated long-lasting repigmentation for up to 4 years in follow-up. The ReCell device (Avita Medical), which automates preparation of non-cultured epidermal cell suspensions, received FDA approval in 2023 for repigmentation of stable depigmented vitiligo lesions in patients aged 18 years, offering a more standardized and operator-independent workflow for MKTP-class procedures.

Discussion

The data reviewed here support a biologically coherent treatment framework in which invasive correction is positioned as the rational next step when immunomodulatory therapies have failed to restore a functional melanocyte reservoir. The IFN-γ-JAK/STAT-CXCL9/CXCL10 axis is no longer merely a molecular curiosity: it is the mechanistic foundation explaining why topical JAK inhibitors such as ruxolitinib cream achieve meaningful repigmentation in active disease, and simultaneously why they cannot restore pigment in fully established lesions where melanocytes have been eliminated entirely. Once the dermal-epidermal junction has been cleared of viable melanocytes, no amount of immune suppression will re-pigment the skin - surgical repopulation is required. Among invasive options, the choice of technique is governed by lesion area, anatomical location, disease subtype, and patient-specific factors. Punch grafting remains widely accessible and technically straightforward, but the cobblestone effect - occurring in up to 27% of patients with 2 mm grafts - limits its use in cosmetically prominent zones unless graft size is reduced to 1.0-1.2 mm. SBEG offers the cleanest cosmetic profile for facial lesions precisely because the donor site heals without visible scarring, but it is time-consuming and cannot cover areas exceeding approximately 50 cm per session without multiple sittings. MKTP, by contrast, provides an elegantly favorable donor-to-recipient ratio of 1:3 to 1:10 and can cover up to 500 cm from a small donor harvest, making it the logical choice for extensive stable vitiligo, particularly segmental variants where the absence of ongoing immune attack creates an especially favorable biological environment. The 66% excellent-outcome rate in segmental vitiligo with MKTP, versus 58.8% in non-segmental cases even with pre-operative phototherapy priming, reflects the fundamental pathophysiological difference between these subtypes: the localized, potentially self-limiting immune process in segmental disease versus the chronic systemic autoimmunity driving non-segmental cases. Pre-operative preparation meaningfully influences

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outcomes. Pre-MKTP narrowband UVB phototherapy primes the recipient site by stimulating residual melanocyte precursors in hair follicles, enhancing graft take and color integration. This is consistent with the finding that younger patients (<24 years) achieve better results, likely reflecting a more abundant follicular melanocyte stem cell pool available for post-operative recruitment. The prognostic role of the Koebner phenomenon cannot be overstated: its presence at time of surgery - even when the disease appears clinically stable - is a powerful negative predictor ($p < 0.001$), and test-grafting prior to full-field surgery remains a strongly advisable precautionary step, with approximately 12% of stable-appearing patients returning negative test results that would contraindicate proceeding. Looking forward, the combination of JAK inhibitor therapy - now including FDA-approved ruxolitinib cream and advanced pipeline molecules such as ritlecitinib and upadacitinib - with surgical repopulation represents the most promising integrated approach. JAK inhibitors neutralize the IFN-γ-mediated positive-feedback loop that would otherwise destroy transplanted melanocytes, while surgery provides the cellular substrate that pharmacotherapy alone cannot generate in fully depigmented skin. This combination strategy is currently under active clinical investigation, though definitive protocol recommendations await the results of ongoing trials.

Vitiligo's irreversible depigmentation results from autoimmune elimination of melanocytes via the IFN-γ-JAK/STAT-CXCL9/CXCL10-CXCR3 axis. When conservative therapy cannot restore the melanocyte reservoir, invasive surgical correction - particularly MKTP and punch grafting - achieves clinically significant repigmentation in well-selected stable patients, with outcomes most favorable in segmental vitiligo and young patients undergoing pre-operative phototherapy preparation.

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