Br J Dermatol 2025; **192**:796–806
https://doi.org/10.1093/bjd/ljae472
Advance access publication date: 14 December 2024

BJD
British Journal of Dermatology
Review Article

Emerging role of regulatory T cells in the immunopathogenesis of vitiligo and implications for treatment

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Abstract

Vitiligo is an autoimmune skin disease that targets pigment-producing melanocytes and results in depigmentation. This disfiguring condition frequently affects visible areas of the body and therefore causes a heavy psychological burden and a decreased quality of life. Although it remains intractable, the ever-growing understanding of its immunopathogenesis has dramatically shaped the treatment paradigm for vitiligo. With the impact of autoreactive cytotoxic T cells explained extensively, accumulating evidence suggests the unique role of regulatory T cells (Tregs) in the immune microenvironment of vitiligo. We systematically reviewed Treg deficiency, instability, reduced vitality and dysfunction in people with vitiligo, combined with novel findings regarding Treg function modulation in autoimmune backgrounds, including metabolic alteration, post-translational modifications and interaction with other immune cells. We further summarized classic and advanced Treg-targeted therapeutics in vitiligo practice and research. Herein, we share up-to-date knowledge of Tregs in vitiligo, providing insights into novel Treg-based therapeutic strategies.

Lay summary

Vitiligo is a skin condition where the immune system wrongly attacks the cells that make the skin's colour (called melanin). This causes patches of skin to lose pigment and appear white. Vitiligo can affect a person's psychological wellbeing due to its visible effects.

Our study focused on understanding the role of a type of immune cell called 'regulatory T cells' (or 'Tregs') in vitiligo. Tregs help regulate the immune system. They are often dysfunctional and unstable in people with vitiligo. Our review reveals that Tregs may not function well in these cases. We also looked at how Tregs are affected by changes in metabolism, changes in proteins and how they work with other immune cells.

Our findings suggest that enhancing the function of Tregs could lead to promising new treatments for vitiligo. This may improve outcomes for people in the future. More research is crucial to explore this and develop treatments that harness the potential of Tregs.

Introduction

Vitiligo is a disfiguring skin disorder characterized by depigmented patches on the skin, scalp and mucosa due to the selective loss of melanocytes, with an estimated prevalence of 1%.[1] Its aetiology involves a complex interplay of genetic predisposition, environmental factors and immune alterations. Stressed melanocytes with inherited defects release damage-associated molecular patterns (DAMPs), exosomes and microRNAs due to environmental stimuli, which trigger the activation of innate immune cells, leading to the recruitment of autoreactive T cells and subsequent immunotoxicity to melanocytes.[2]

Regulatory T cells (Tregs) – derived from the differentiation of initial $CD4^+$ T cells – inhibit aberrant or excessive immune responses of $CD4^+$ and $CD8^+$ T cells, thus playing a pivotal role in maintaining immune tolerance and homeostasis in autoimmune diseases. Although the exact functions of Tregs in the pathogenesis of vitiligo remain largely unknown, researchers have identified an aberrant quantity and quality of Tregs in the peripheral blood and skin lesions of patients with the disease,[3] which is closely correlated with the proliferation and activation of cytotoxic T lymphocytes (CTLs).[4]

Herein, we review the current evidence on Treg alterations in vitiligo and present up-to-date knowledge of the immunopathogenesis of vitiligo with a particular focus on Tregs and their interaction with other immune cells (Figure 1). Moreover, classic and advanced Treg-targeted therapeutics in vitiligo practice and research are summarized to highlight the vital role of Tregs in the treatment of vitiligo, with the hope of highlighting new targets for future therapeutic interventions.

Accepted: 28 November 2024
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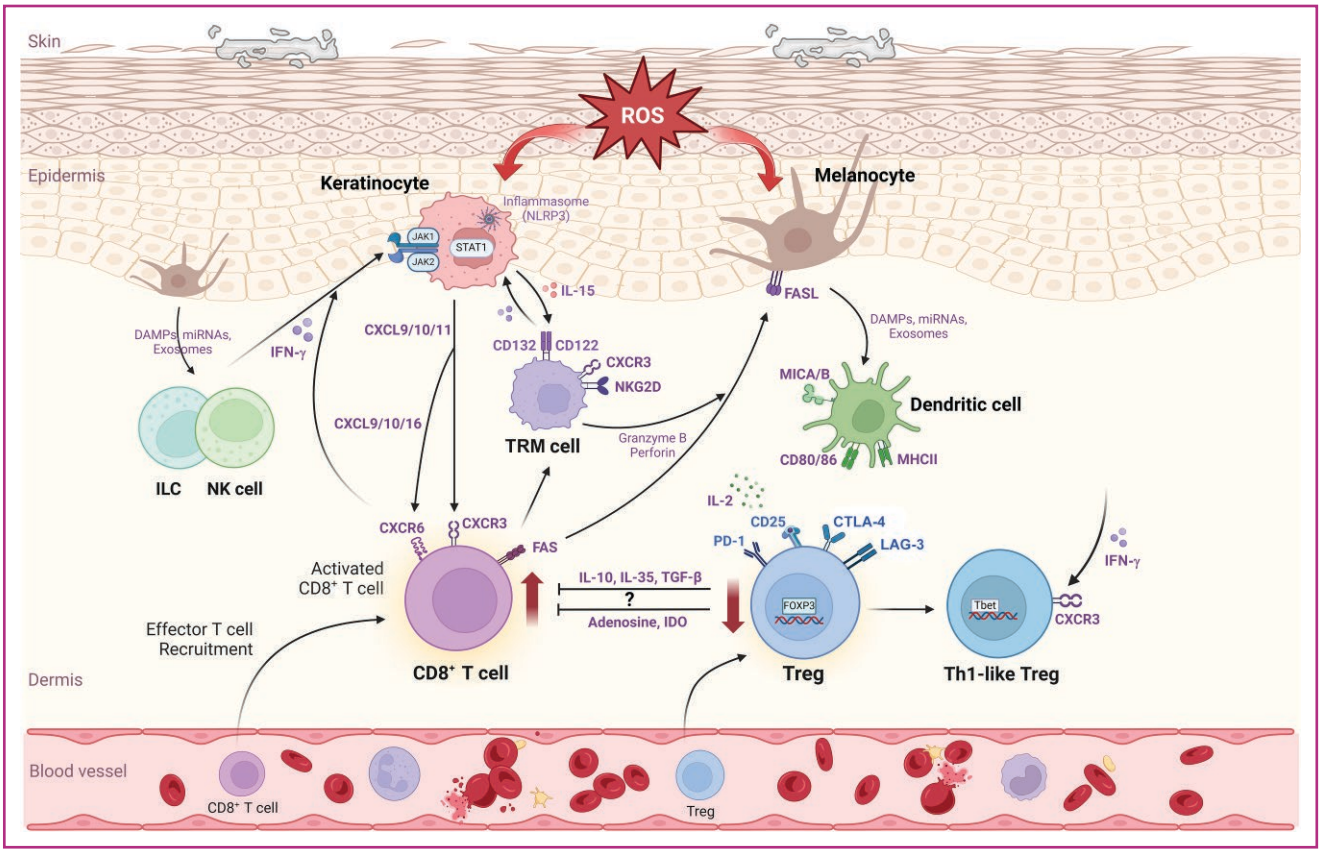

Figure 1 The role of regulatory T cells (Tregs) and crosstalk with other immune cells in vitiligo. Stressed melanocytes trigger the activation of innate immune cells, initiating an abnormal immune response in vitiligo mainly centred on the activation of Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway by the binding of interferon (IFN)-γ with its receptor. CD8⁺ T cells are recruited to the skin by chemotactic factors produced by keratinocytes, and express CD69 and CD103 upon activation, differentiating into CD8⁺ tissue-resident memory T (TRM) cells. CD8⁺ T cells and TRM cells exert cytotoxic effects against melanocytes, contributing to their destruction. TRM cells sustain the presence of vitiligo in the skin by relying on the interleukin (IL)-15 pathway and can further enhance inflammation through the release of proinflammatory cytokines. Decreased frequency and dysfunctional Tregs display an insufficient immunosuppressive effect and even a proinflammatory phenotype due to instability. DAMP, damage-associated molecular pattern; FASL, Fas ligand; IDO, indoleamine 2,3-dioxygenase; LAG-3, lymphocyte activation gene 3; MHC, major histocompatibility complex; MICA/B, MHC I chain-related protein A and B; miRNA, microRNA; NKG2D, natural killer group 2, member D; NLRP3, NLR family pyrin domain containing 3; PD-1, programmed cell death protein 1; ROS, reactive oxygen species; Tbet, T-box expressed in T cells; TGF, transforming growth factor; Th, T helper. Created with BioRender.com.

Definition and function of regulatory T cells

Classification and phenotypic features

Naturally occurring CD4⁺ Tregs, which specifically express the transcription factor Forkhead box P3 (FoxP3) and surface receptor CD25, are a functionally distinct T-cell subpopulation actively engaged in the maintenance of immunological homeostasis. Thymus-derived Tregs constitute the majority of FoxP3⁺ Tregs in the periphery, while some conventional T cells (Tconvs) in the peripheral sites could gain stable FoxP3 expression and differentiate into peripherally derived Tregs.[5] Tconvs can also differentiate *in vitro* to express FoxP3 under special conditions, forming *in vitro*-induced Tregs.[5]

Functions of regulatory T cells in skin homeostasis

Skin-resident Tregs, often characterized as memory Tregs due to their expression of memory T-cell markers like CD45RO, are integral to the modulation of immune responses following antigen exposure.[6] Apart from attenuating inflammatory responses, skin-resident Tregs can also promote skin wound repair, maintain tolerance to commensal skin microbiota and assist follicular regeneration.[7] Selectively blocking Treg function in the skin has been shown to cause severe cutaneous inflammation in a mouse model.[8] Moreover, studies have found that selective depletion of skin Tregs results in T cell-mediated inflammation of hair follicles, indicating a vital role of skin Tregs in the immunological protection of hair follicle stem cells.[9]

Immunopathogenesis of vitiligo: focusing on the interplay of regulatory T cells with other immune cells

CD8⁺ cytotoxic T lymphocytes

Excessive activation of CD8⁺ CTLs results in cytotoxicity toward melanocytes via recognition of melanocyte differentiation antigens such as tyrosinase, gp100 and MART-1 (melanoma-associated antigen recognized by T cells).[10]

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Keratinocytes secrete CXCL9, CXCL10 and CXCL16, which – after binding with receptors CXCR3 or CXCR6 – chemotactically attract CD8+ T cells to the epidermis.[11–13] CD8+ CTLs expressing cytotoxic molecules like interferon (IFN)-γ, granzyme B and perforin disrupt melanocytes via the Fas–Fas ligand pathway.[4] Although it is well established that Tregs can suppress effector T cells via inhibitory cytokines, cytolysis, metabolic disruption and modulation of dendritic cell (DC) function,[14,15] the underpinnings of the impaired immunosuppressive effect of Tregs on CD8+ CTLs in vitiligo remain largely unknown and need to be further validated. The activation and persistence of CD8+ tissue-resident memory T (TRM) cells in the skin are influenced by the ongoing activity of these CD8+ CTLs, highlighting the need to consider both cell types in the context of vitiligo pathology.

Tissue-resident memory T cells

TRM cells play a pivotal role in vitiligo recurrence, with 40% of patients experiencing relapses in treated areas.[16] Melanocyte-specific CD8+ T cells in lesions could exhibit a TRM phenotype (CD69+CD103+), producing IFN-γ and tumour necrosis factor-α.[17] Targeting interleukin (IL)-15 signalling with anti-CD122 antibody reversed depigmentation in a vitiligo mouse model by inhibiting IFN-γ production and depleting TRM cells.[18] A recent study revealed that TRM-Tregs (CD103+CD4+CD25+) and antigen-specific Tregs (GARP+CD4+CD25+) were unable to suppress CD8+ TRM cell proliferation and cytotoxicity toward melanocytes due to paucity and functional defects.[19] Additionally, replenishing TRM-Tregs might directly promote repigmentation by protecting melanocyte stem cells from TRM cell-mediated damage.

Dendritic cells

Oxidative stress activates innate immune cells like DCs, natural killer (NK) cells and innate lymphoid cells (ILCs), initiating the onset of vitiligo. Stress-induced inducible heat-shock protein 70 (HSP70i) triggers local DC subgroups, promoting inflammation and disrupting immune tolerance, thereby fuelling the autoimmune response in vitiligo.[20] DCs influence the genesis, maturation and function of Tregs, while the function of DCs relies on Treg-mediated immune regulation. Cytotoxic T lymphocyte antigen 4 (CTLA-4) on Tregs binds CD80/86 on DCs,[21] downregulating the expression of indoleamine 2,3-dioxygenase (IDO) and impeding Treg proliferation.[22] Meanwhile, LAG-3 (lymphocyte activation gene 3), expressed by Tregs, could bind major histocompatibility complex II and inhibit DC activation.[23] Further research focusing on Treg–DC interactions in the context of vitiligo might provide novel targets for enhancing the immunosuppressive functions of Tregs.

Innate lymphoid and natural killer cells

Elevated levels of ILC-1 and NK cells, along with their sensitivity to DAMPs such as HSP70i and high mobility group box 1 protein (HMGB1), have been found in the blood and skin of patients with vitiligo.[24] Studies have indicated that Tregs exhibit impaired suppression of NK cells in patients with active vitiligo, resulting in NK cell overactivation and melanocyte destruction.[25] Meanwhile, NK and ILC-1 cells contribute to the type I-skewed inflammatory microenvironment by secreting IFN-γ and expressing the transcription factor Tbet (T-box expressed in T cells),[24] which might interfere with Treg stability. Breaking the vicious cycle by modulating the interplay between Tregs and ILCs might curb the progression of vitiligo.

Current evidence for regulatory T-cell alterations in vitiligo

Insufficient frequency of regulatory T cells in vitiligo

Most researchers have reported decreased frequencies of Tregs in skin lesions and in the peripheral blood of patients with vitiligo compared with healthy controls.[3] Patients with early-onset vitiligo (aged 1–20 years) have also been found to have fewer circulating Tregs than those with later-onset disease.[26] Furthermore, patients with active-stage vitiligo exhibited fewer circulating Tregs than those with stable disease.[27] These observations suggest that a deficiency in Tregs contributes to the onset and progression of vitiligo, and replenishing Tregs could be a possible therapeutic option. The role of Tregs in the vitiligo microenvironment involves multiple mechanisms (Figure 2).

Regulatory T-cell dysfunction in vitiligo

Inhibitory cytokines

Tregs produce inhibitory cytokines such as IL-10, transforming growth factor (TGF)-β and IL-35 to inhibit the activation of effector T cells. In-depth studies in vitiligo have found deficiencies in these cytokines, with dysregulated levels correlating with disease stage and affected skin areas. Specifically, decreased concentrations of IL-10 have been found in vitiligo lesions vs. nonlesional areas,[28] and also in patients with active disease vs. stable disease.[29] Similarly, lower serum TGF-β levels are positively correlated with disease duration and the percentage of body surface area involvement, indicating that altered cell immunity might facilitate melanocyte cytotoxicity in vitiligo.[30]

Skin-homing capacity

Chemokine ligand–receptor interactions, such as CCL1–CCR8, CCL21–CCR7 and CCL22–CCR4, have been implicated in guiding Treg migration. Overexpression of CCL22 in the skin of vitiligo-prone mice has been found to result in significantly reduced depigmentation with infiltration of CCR4+ Tregs.[31] Conversely, CCR6-deficient Tregs were found to exhibit impaired migration in a vitiligo mouse model, resulting in severe depigmentation.[32] Moreover, single-cell RNA sequencing (scRNAseq) has found that CCL5–CCR5 signalling mediates a chemokine circuit between effector CD8+ T cells and Tregs in vitiligo skin samples. CCR5 on Tregs drives their positioning near CCL5-secreting CD8+ T cells and facilitates their interaction.[33] Targeting these chemokines could serve as a promising therapeutic strategy for vitiligo by recruiting circulating Tregs and restoring immune tolerance.

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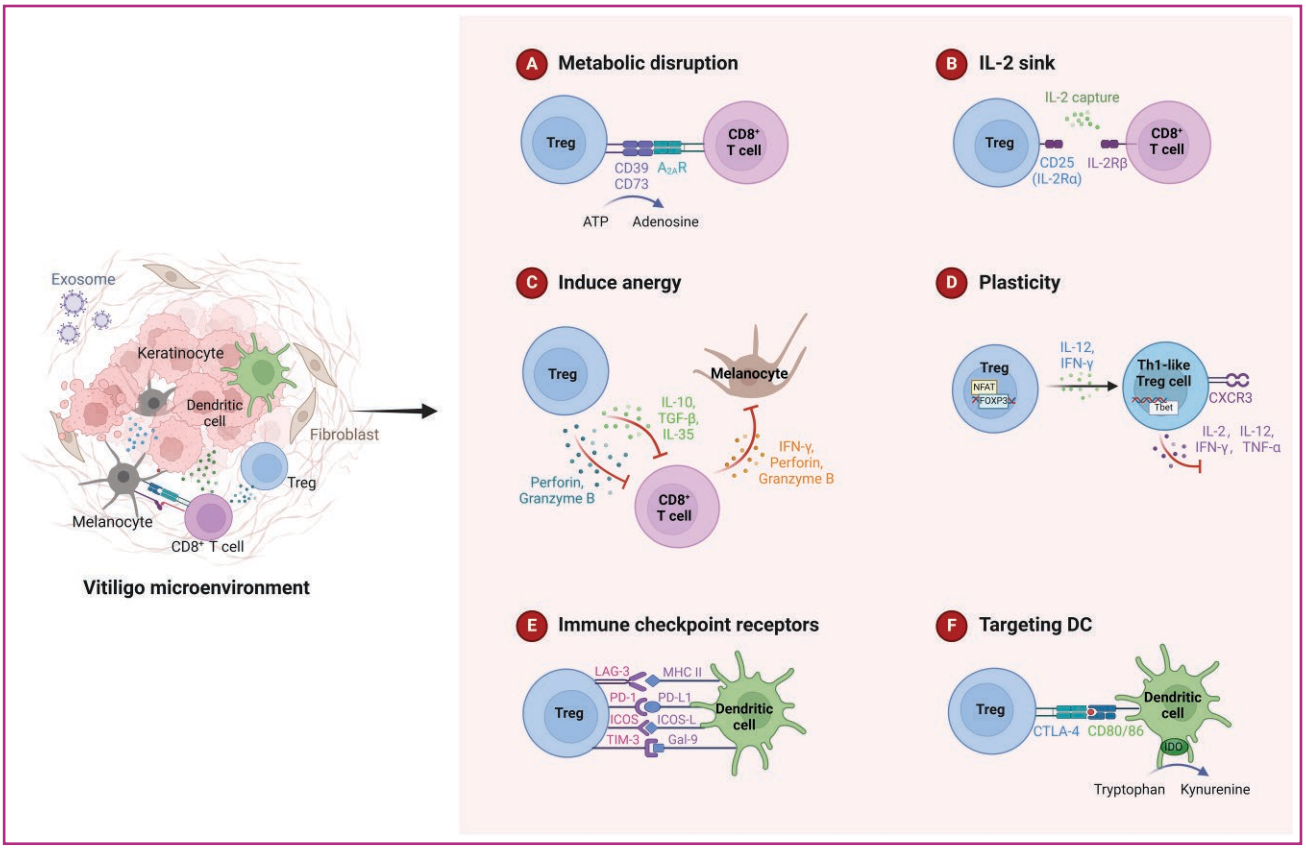

Figure 2 The role of regulatory T cells (Tregs) in the vitiligo microenvironment. (A) Metabolic disruption. Adenosine receptor (A_{2A}) mediated immunosuppression. Adenosine triphosphate (ATP) is converted to adenosine monophosphate (AMP) by CD39 and further to adenosine by CD73, inhibiting CD8+ T-cell function. (B) Interleukin (IL)-2 sink. Treg-derived CD25 consumes IL-2, reducing CD8+ T-cell activation and promoting apoptosis. (C) Induction of anergy. Production of inhibitory cytokines, including IL-10, IL-35 and transforming growth factor (TGF)-β. Direct cytotoxic effects occur through the production of granzyme B and perforin and consequent cell apoptosis. (D) Plasticity. Under inflammatory stimuli, Tregs may co-express T helper (Th) cell lineage-defining transcription factors, such as T-box expressed in T cells (Tbet), leading to the acquisition of proinflammatory functions. (E) Immune checkpoint receptors. Immunoregulation through lymphocyte activation gene 3 (LAG-3)–major histocompatibility complex (MHC) class II, programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and inducible co-stimulator (ICOS)–ICOS ligand (ICOSL) pathways, inhibiting CD8+ T cells and promoting Treg activation. (F) Targeting dendritic cells (DCs). Cytotoxic T lymphocyte antigen 4 (CTLA-4) expressed on Tregs interacts with co-stimulatory molecules CD80/86 preventing DCs from effectively stimulating CD8+ T cells. Gal-9, galectin-9; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; LAG-3, lymphocyte activation gene 3; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; TNF, tumour necrosis factor. Created with BioRender.com.

Transcription factors

The expression of the key transcription factor FoxP3, the dynamic assembly of transcriptional complexes and post-translational modifications collectively contribute to the development and stability of Tregs and their immunosuppressive capabilities.[34,35] Studies have demonstrated downregulated FoxP3 levels in the peripheral blood and skin lesions of patients with vitiligo compared with healthy controls, with even lower levels in patients with active disease vs. those with stable disease, further highlighting the role of FoxP3 in the impaired inhibitory function of Tregs in vitiligo.[3] Accessory transcription factors like nuclear factor of activated T cells (NFAT) also participate in imprinting Treg specification and function. Giri *et al.* discovered disruptions in the Ca^{2+}–calmodulin–calcineurin–NFAT signalling pathway in Tregs from patients with vitiligo, leading to decreased FoxP3, IL-10 and CTLA-4 expression, and weakened Treg inhibitory effects, thereby contributing to the pathogenesis of vitiligo.[36] The molecular mechanisms behind FoxP3 downregulation remain largely unknown. Genetic studies have revealed that polymorphisms of *FOXP3* (positions –3279, –6054 and –924) in the Chinese Han population may be associated with vitiligo onset.[37] Subsequent studies found that polymorphisms in *NFATC2* in a Gujarat population may downregulate NFAT expression and increase the risk of generalized vitiligo.[38] Notably, post-translational modifications through phosphorylation, ubiquitination and acetylation of FoxP3 play crucial roles in dynamically modulating Treg stability and function in autoimmune diseases.[35] Further research is needed to elucidate their impact on the pathogenesis of vitiligo.

T-cell plasticity and T helper 1-like regulatory T cells in vitiligo

Tregs can adapt to T helper (Th)-polarizing environments and exhibit functional heterogeneity, known as Treg plasticity, which could undergo functional and phenotypic transformation such as Th1-like (IFN-γ$^+$Tbet$^+$), Th2-like [GATA3$^+$IRF4$^+$ (IFN regulatory factor 4)], Th17-like [IL-17$^+$RORγ$^+$ (RAR-related orphan receptor gamma)] and T follicular helper-like (Bcl-6$^+$) Tregs.[39] A recent scRNAseq study found that Tregs expressed proinflammatory IFN-γ in the lesional skin of

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Table 1 Recent clinical trials for vitiligo treatment

Treatment	Classification	Mechanism	Study (start year/ country/NCT)	Status/phase	Study design		Results
					Drug intervention	Types	
VitD	VitD3	Stimulation of tyrosinase activity; melanocyte regeneration and immunosuppression	2018/Korea/ 05364567	Completed/NA	VitD deficiency: 200 000 IU cholecalciferol injection, once at baseline	OL, randomized, parallel assignment	NA
	VitD		2021/ Mexico/04872257	Completed/NA	VitD 5000 IU for 6 months (oral, daily)	Triple-blind, randomized, parallel assignment	NA
Low-dose IL-2	IL-2 muteins	Specific activation and amplification of Tregs; immunosuppression	2023/USA/ 06113328	Recruiting/IIA	MK-6194 administered SC	Quadruple-blind, multicentre, noncontrolled, nonrandomized, parallel assignment	NA
Anti-IL-15 biologics	Anti-IL-15 mAb	Blockage of IL-15 signalling; immunosuppression and TRM cell elimination	2020/USA/ 04338581	Completed/II	Injection of 300 mg AMG 714, Q2W	Quadruple-blind, randomized, parallel assignment	Proportion of participants achieving F-VASI ≥ 35 at W24
PDEi	PDE4i	Excessive degradation of cAMP prevention; melanocyte regeneration and immunosuppression	2017/USA/ 03123016	Completed/II	Apremilast 30 mg orally, twice daily	OL, single-group assignment	NA
			2017/France/ 03036995	Completed/II	Apremilast 30 mg orally, twice daily	Triple-blind, parallel assignment	NA
			2022/USA/ 05298033	Active, not recruiting/IIA	PF-07038124 0.01% vs. crisaborole 2% topical ointment, twice daily	Quadruple-blind, factorial assignment	NA
PI3 K/Akt/ mTOR	mTORi	Induction of Treg expansion; melanocyte regeneration and immunosuppression	2022/USA/ 05342519	Active, not recruiting/II	0.1% or 0.001% topical rapamycin, twice daily	Quadruple-blind, randomized, parallel assignment	NA
	α-MSH analogue	Stimulation of pigmentation and increased proliferation of melanocytes; melanocyte regeneration	2022/USA/ 05210582	Recruiting/II	16 mg afamelanotide implant SC every 28 days	OL, single group assignment	NA
JAK/STAT	TYK2i	Disruption of cytokine signalling (IFN-γ); immunosuppression	2024/France/ 06327321	Recruiting/III	Deucravacitinib 12 mg daily	Single-blind, randomized, parallel assignment	NA
	JAK1i		2020/China/ 04774809	Terminated/II/ III	Low-/high-dose SHR0302 ointment, twice daily	Quadruple-blind, randomized, parallel assignment	NA
	Type I IFN receptor antagonist		2023/France/ 05917561	Recruiting/ phase II	Anifrolumab 300 mg/ month for 36W	Double-blind, multicentre, parallel double-blind randomized phase II prospective study, parallel assignment	NA
	JAK3, JAK1/ TYK2i		2022/multicountry/ 03715829	Completed/ phase IIB	Ritlecitinib (PF-06651600) and brepocitinib (PF-06700841) oral tablet taken once daily for 24W	Double-blind, randomized, multicentre, parallel assignment	To compare efficacy of ritlecitinib and brepocitinib combined with or without phototherapy
CTLA-4 fusion protein	Selective T-cell co-stimulator	Inhibit T-cell activation, immunosuppression	January 2015/ USA/02281058	Unknown/I	Abatacept 125 mg administered SC weekly for 24W	OL, single group assignment	NA

cAMP, cyclic adenosine monophosphate; CTLA-4, cytotoxic T lymphocyte antigen 4; F-VASI, Facial Vitiligo Area Scoring Index; IFN, interferon; IL, interleukin; JAK, Janus kinase; JAKi, JAK inhibitor; mAb, monoclonal antibody; MSH, melanocyte-stimulating hormone; mTOR, mammalian target of rapamycin; mTORi, mTOR inhibitor; NA, not available; OL, open label; PDEi, phosphodiesterase inhibitor; PDE4i, phosphodiesterase 4 inhibitor; PI3 K, phosphoinositide 3-kinase; Q2W, every 2 weeks; SC, subcutaneously; STAT, signal transducers and activators of transcription; Treg, regulatory T cell; TRM, tissue-resident memory T cell; TYK2i, tyrosine kinase 2 inhibitor; VitD, vitamin D; W, week.

patients with vitiligo.[33] Feng *et al.* demonstrated that IFN-γ-producing Tregs might lose their suppressive capabilities as they transition to terminally differentiated effector cells.[40] Chen *et al.* further clarified the IFN-γ$^+$ Treg cells in vitiligo as Tbet$^+$CXCR3$^+$FoxP3$^+$ Th1-like Treg cells, which had an increased chemotactic response to CXCL10 and CXCL16.[41] Intriguingly, serum from patients with vitiligo can convert bona fide Tregs from healthy individuals into Th1-like Tregs, suggesting that the type I-skewed inflammatory microenvironment in vitiligo promotes the phenotypic shift of Tregs toward a proinflammatory state.[41] Another study demonstrated that Th1-like Tregs promote the generation of CD8$^+$ TRM cells through proximity to effector T cells and integrin-β8-mediated TGF-β availability.[42] The role of Th1-like Tregs in autoimmune disease as friend or foe has remained controversial, with further clarification of the underlying

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molecular mechanism and their impact on CD8+ CTLs and memory T cells required.

Immunometabolism and its implications in vitiligo

The relationship between inflammation, oxidative stress and metabolism is often linked to the development and progression of autoimmune diseases.[43] Epidemiological studies have suggested an increased risk of glucose and lipid metabolism disruption in people with vitiligo vs. the general population.[44] At the cellular level, oxidative stress disrupts glycolipid metabolism in melanocytes, leading to the production of abnormal reactive oxygen species and exacerbation of oxidative damage.[43] This stress could shift the tricarboxylic acid cycle to a reductive state, increasing DNA methylation and suppressing Treg-associated gene expression and function.[45] It would be worthwhile exploring how metabolic alteration in vitiligo modulates immune cell function, as this could open an attractive new therapeutic path from a metabolic perspective.

Regulatory T cells in the treatment of vitiligo

Treatment strategies for vitiligo focus on modulating immune responses to curb disease progression in progressive vitiligo and shielding against oxidative stress by enhancing melanocyte repair and hastening their regeneration during stable phases. It is currently well accepted that the generation and preservation of functional antigen-specific Tregs are vital for the restriction of immune responses and protection of melanocytes. To illustrate the advances in vitiligo treatment, we thoroughly reviewed ongoing clinical trials and published studies, which are summarized in Table 1 and Table 2, respectively. A detailed description of Treg-related and targeted therapies is provided below.

Impact of existing vitiligo therapies on regulatory T cells

Phototherapy

Phototherapy includes psoralen + ultraviolet A (PUVA) and narrowband ultraviolet B (NB-UVB) treatments. These are the primary therapeutic modalities for generalized vitiligo. For localized disease, 308-nm monochromatic excimer laser therapy is used. NB-UVB could induce T-cell apoptosis, downregulate inflammatory factors, and upregulate IL-10 and aryl hydrocarbon receptor (AhR),[46,47] shifting the balance toward Tregs.[48] Ultraviolet light effectively activates precursor melanocytes, making phototherapy the standard treatment for promoting melanocyte regeneration and mitigating T-cell immune damage in vitiligo.

Corticosteroids

Topical corticosteroids are the primary first-line treatment for vitiligo, with oral steroid minipulse therapy used for people with rapidly spreading disease. Corticosteroids exert broad anti-inflammatory, antimitosis and immunosuppressive effects.[49] Studies using autoimmune and allergic inflammation mouse models have shown that Tregs are irreplaceable glucocorticoids target cells *in vivo*.[50] Dexamethasone has been shown to induce miR-342-3p specifically in Tregs, which further targeted the mammalian target of rapamycin complex 2 (mTORC2) component and regulated metabolic programming in Tregs.[50] These results indicate that the frequency and stability of Tregs might influence the treatment response to systemic corticosteroids in patients with vitiligo.

Calcineurin inhibitors

Topical calcineurin inhibitors (TCIs), including pimecrolimus and tacrolimus (0.3% and 1%), are used off-label for vitiligo, especially for lesions on the face, neck and other areas with thin skin. The immunosuppressive action of TCIs involves inducing IL-10 and reducing IL-2 and IL-2 receptor expression by inhibiting NFAT, selectively interfering with T-cell function.[51]

Janus kinase inhibitors

With increasing evidence of the vital role of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway in the pathogenesis of vitiligo, JAK inhibitors (JAKi) are promising therapeutic options. JAKi may block IFN-γ signalling, preventing melanocyte damage caused by the recruitment of CD8+ T cells.[52] Although JAKi have shown promise in modulating immune responses in vitiligo by blocking IFN-γ signalling, their effects on Tregs remain largely unexplored. Future studies on how JAK inhibition might influence Treg frequency, stability and function in vitiligo would be of interest. The JAK1/2 inhibitor ruxolitinib has been approved by the U.S. Food and Drug Administration for the treatment of patients with nonsegmental vitiligo aged ≥ 12 years.[53] Several oral JAKi, including upadacitinib (JAK1), povorcitinib (JAK1) and ritlecitinib (JAK3/Tec), are currently in phase III clinical trials.[49] Future studies comparing different JAKi and their synergistic effects with phototherapy, and assessing long-term safety, would provide more practical knowledge for clinical applications.

Potential treatment affecting regulatory T cells in vitiligo

Vitamin D

Vitamin D (VitD) is a key modulator of immune responses and cellular functions, especially in the skin. The association between decreased VitD levels and vitiligo suggests a potential role for VitD supplementation in controlling disease stability and enhancing repigmentation.[54] VitD affects melanocyte differentiation and function through its impact on tyrosinase and modulates immune cell activity via the VitD receptor.[55] VitD and IL-2 jointly suppress the production of inflammatory cytokines by T cells and promote Tregs expressing CTLA-4 and FoxP3,[56] thus aiding in the suppression of autoimmune responses and maintaining immune balance. Studies indicate that VitD deficiency in genetically predisposed individuals could impair self-tolerance by compromising the regulation of DCs, Tregs and Th1 cells.[57] Hence, the effects of VitD on Treg development and immune cell survival status offer therapeutic potential in vitiligo management.

Low-dose interleukin (IL)-2 and IL-2 mutein

Restoration of Treg fitness and/or expansion of their numbers using low-dose IL-2, the main cytokine that drives Treg survival and function, has demonstrated clinical efficacy in

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Table 2 Summary of the efficacy and adverse events (AEs) of emerging vitiligo therapies that target regulatory T cells

Reference	Study design (no. of patients)	Intervention and duration	Efficacy	AEs	Implications
Garza[87]	RCT (n=26)	NB-UVB+VitD vs. NB-UVB+placebo for 24W	QoL improvement in both groups	No VitD intoxication was reported	VitD supplementation did not add any benefit to NB-UVB treatment
Juntongjin[88]	RCT (n=13/26 hands)	308-nm excimer light+calcipotriol vs. 308-nm excimer light+clobetasol, crossover at 12W	Greater improvement with the calcipotriol-based regimen vs. clobetasol-based regimen	No specific quantity mentioned	Combination treatment with excimer light+topical VitD3 analogue was effective for acral vitiligo
Khullar[89]	RCT (n=27)	NB-UVB+calcipotriol vs. NB-UVB+placebo, crossover for 24W	Slightly better repigmentation on NB-UVB side	7 patients, all mild	Calcipotriol did not add any benefit to NB-UVB treatment
Abdel Latif[90]	RCT (n=44)	VitD3 analogue+steroid vs. 308-nm MEL for 12W each	Significant improvement in both treatment modalities, but without significant differences	14 patients, all mild	Topical combination of VitD3 analogue+steroid or 308-nm MEL gave comparable results
Sharma[91]	RCT (n=37)	Standard treatment vs. standard treatment+apremilast for 12W each	Greater reduction in VASI, BSA, DLQI and BMI in the add-on apremilast group vs. standard treatment group	16 mild (1 depression) in the add-on apremilast group; 7 mild in the control group	Treatment with add-on apremilast accelerated clinical improvement and reduced disease progression
Kim[92]	RCT (n=28)	NB-UVB vs. apremilast vs. NB-UVB+apremilast for 16W each	Greater reduction in VASI with combination vs. either monotherapy	4 patients, severity not stated	Apremilast+NB-UVB may expedite repigmentation
Khemis[93]	RCT (n=80)	NB-UVB+apremilast vs. NB-UVB+placebo, crossover at 24W	Similar mean reduction in VASI in both groups	7 mild, 2 serious (1 benign tumour of the amygdala and 1 suicide attempt)	Apremilast did not add any benefit to NB-UVB treatment
Majid[94]	Case series (n=13)	Apremilast 30 mg twice daily for 3 months	Disease stabilization in all cases; repigmentation in 8/13 patients (62%)	2 patients, both mild	Apremilast effective in halting disease and promoting repigmentation
Toh[95]	RCT (n=18)	NB-UVB+afamelanotide implants vs. NB-UVB+placebo for 7 months each	Greater reduction in VASI with combination vs. placebo	No specific quantity mentioned	Afamelanotide did add some benefits to NB-UVB treatment
Lim[96]	RCT (n=55)	NB-UVB+afamelanotide vs. NB-UVB for 6 months each	Higher percentage of and earlier time to repigmentation with combination vs. either monotherapy	19 mild, 2 serious (hypertension) in the add-on afamelanotide group; 22 mild in the control group	Afamelanotide in combination with NB-UVB may expedite repigmentation

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; MEL, monochromatic excimer light; NB-UVB, narrowband ultraviolet B; QoL, quality of life; RCT, randomized controlled trial; VASI, Vitiligo Area and Severity Index; VitD, vitamin D; W, weeks. F-VASI, Faced-Vitiligo Area Scoring Index.

early clinical trials of autoimmune diseases.[58] The application of low-dose IL-2 may help selectively expand Tregs or enhance their suppressive activity *in vivo*, restoring immune balance, thus ameliorating symptoms in patients with vitiligo. Moreover, genetically modified IL-2 with an extended half-life and higher affinity for CD25 subunits has been shown to achieve better stability and increased selectivity for Tregs.[59] A modified IL-2 mutein MK-6194, engineered for selectively targeting Tregs, is currently being tested for vitiligo (NCT06113328). Nevertheless, the potential side-effects of immunosuppression and the need for precise regulation of Treg activity need to be noted.

Mammalian target of rapamycin inhibitor

Mammalian target of rapamycin (mTOR) serves as a pivotal regulator of cell growth, proliferation and metabolism, of which dysregulation is linked to various autoimmune and inflammatory skin disorders, including vitiligo.[60] Classical mTOR inhibitors such as rapamycin/sirolimus partially inhibit mTORC1 and activate Akt through a feedback loop, thereby facilitating repigmentation of affected skin areas in vitiligo.[61] More importantly, rapamycin together with autoantigen could induce immunological tolerance and promote Tregs in multiple autoimmune diseases. *In vivo* and *in vitro* studies have indicated that rapamycin treatment leads to an expansion of Treg numbers in skin lesions, resulting in sustained remission of vitiligo.[62,63]

Activating Wnt/β-catenin signalling pathway

Upregulation of Wnt/β-catenin signalling could potentially attenuate vitiligo progression by protecting melanocytes from oxidative stress damage, inhibiting $CD8^+$ T-cell differentiation and enhancing Treg function.[64] Stabilization of β-catenin in Tregs can prolong survival time and increase

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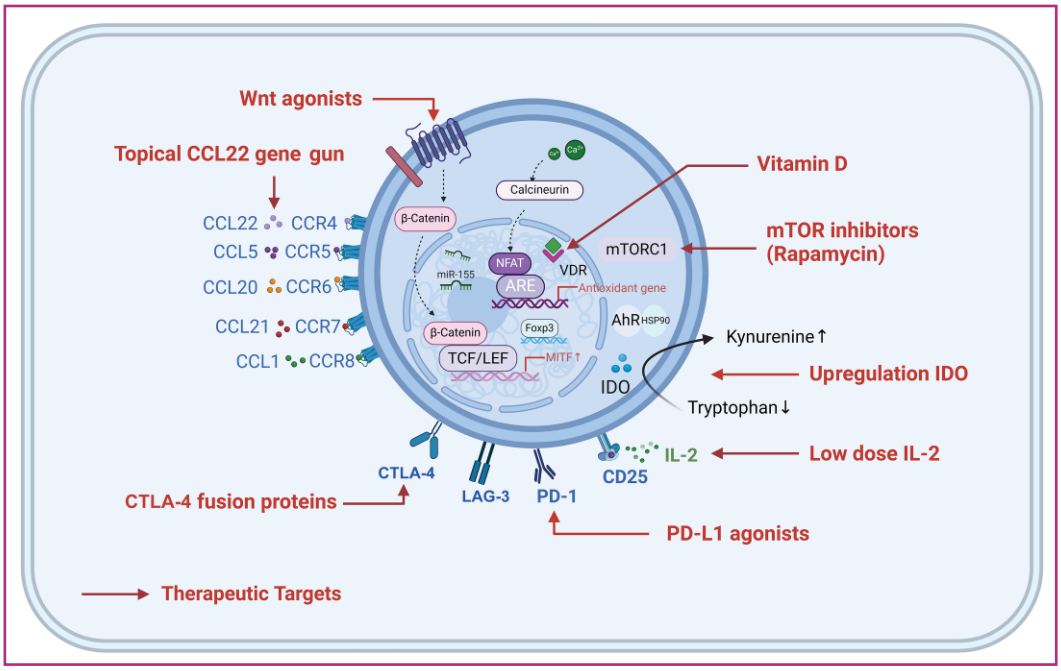

Figure 3 Immunomodulatory effect of emerging vitiligo therapies on regulatory T cells (Tregs). Emerging therapies for vitiligo affect Tregs by enhancing their quantity, stability and differentiation. Immunomodulatory agents such as cytotoxic T lymphocyte antigen 4 (CTLA-4) fusion proteins (abatacept), vitamin D, low-dose interleukin (IL)-2 and IL-2 mutein (MK-6194), mammalian target of rapamycin (mTOR) inhibitors (rapamycin) and topical CCL22 gene gun delivery have been investigated in clinical trials and/or animal models for vitiligo. Hypothetical targets, including the Wnt/β-catenin signalling pathway, indoleamine 2,3-dioxygenase (IDO)/aryl hydrocarbon receptor (AhR) signalling pathway and programmed death-ligand 1 (PD-L1) fusion proteins, may also interfere with Treg function in vitiligo immunopathogenesis. However, these targets require further investigation and validation. ARE, antioxidant response element; HSP, heat shock protein; LEF, lymphoid enhancer-binding factor; MITF, microphthalmia-associated transcription factor; mTORC, mammalian target of rapamycin complex; NFAT, nuclear factor of activated T cells; PD-1, programmed cell death protein 1; TCF, T-cell factor; VDR, vitamin D receptor. Created with BioRender.com.

suppression activity.[65] Meanwhile, β-catenin interacts with T-cell factor/lymphoid enhancer factor transcription factors in DCs, resulting in the expression of anti-inflammatory cytokines that induce Tregs.[66] Further evidence supports the involvement of the Wnt/β-catenin pathway in the proliferation, migration and differentiation of melanocytes.[67] The difficulty of repigmenting certain areas, such as palmoplantar skin, may be attributed to the abundant secretion of DKK1 (Dickkopf-related protein 1; a Wnt inhibitor) by dermal fibroblasts in such regions.[68] Strategies aimed at activating the Wnt/β-catenin signalling pathway through localized treatments hold promise for overcoming these challenges and achieving repigmentation in difficult-to-treat regions.

Modulating IDO/aryl hydrocarbon receptor signalling pathway

IDO is an immune-regulatory enzyme that catalyses the conversion of tryptophan into kynurenine (KYN), a process intricately linked to T-cell activation and immune tolerance mediated by Tregs. When manifested on DCs, IDO drives the differentiation of naïve CD4+ T cells towards a FoxP3 phenotype, thereby amplifying Treg-mediated suppression of effector T cells and averting the transition of Tregs into proinflammatory cells.[69,70] KYN also acts as a ligand for AhR, which plays diverse roles in skin physiology and pathology, including melanogenesis, inflammation and cancer.[71] Recent research has shed light on the intricate interplay between AhR and IDO in governing T-cell function across various autoimmune diseases.[72] Studies have shown downregulated expression of AhR in vitiligo skin lesions.[71] Noteworthy observations in AhR knockout mice include reduced tail skin melanocytes, decreased pigmentation and lower IL-10 production by Tregs.[73] Moreover, the JAKi tofacitinib has been found to decrease the T-cell stimulatory capability of DCs and increase IDO expression by inhibiting type I IFN signalling, suggesting a novel mechanism for modulating DC differentiation.[74]

Topical CCL22 gene gun delivery

Dermal CCL22 is an immunosuppressive chemokine derived from macrophages.[75] Decreased expression of CCL22 in vitiligo skin suggests a defect in Treg homing,[76] while introducing CCL22 into vitiligo skin lesions via gene gun therapy has been found to promote the recruitment of Tregs to the lesions, reduce reactive T cells against melanocytes and significantly diminish pigment loss in a mouse model.[31,77] However, the validation of numerous perspectives from preclinical studies is yet to be done in larger human cohorts.

Immunomodulatory agents: programmed death ligand 1 and cytotoxic T lymphocyte antigen 4 fusion proteins

Vitiligo has emerged as a prominent adverse reaction to immune checkpoint inhibitors, specifically programmed cell death protein 1 (PD-1) and CTLA-4 inhibitors.[78] PD-1 and CTLA-4 serve as negative regulators of T cells, and their inhibition can lead to excessive activation of CD8+ T cells, which attack melanocytes and trigger vitiligo. Conversely,

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abatacept – a CTLA-4 fusion protein that has proved effective in reducing T-cell activity and alleviating symptoms of rheumatoid arthritis and severe acute graft-versus-host disease[79,80] – is now being evaluated in a pilot study of vitiligo (NCT02281058). Meanwhile, programmed death ligand 1 (PD-L1) fusion protein halted depigmentation in Pmel-1 vitiligo mice by significantly increasing Tregs in the skin and decreasing melanocyte-reactive T cells.[81] Nevertheless, increased PD-1 expression has been observed in peripheral Tregs and CD8+ T cells.[76,82] Further research is warranted to elucidate the impact of PD-1/PD-L1 signalling on different T-cell subsets to ascertain treatment efficacy.[83]

Antigen-specific regulatory T cells

Replenishing Tregs has become a new therapeutic approach to treating autoimmune diseases. Recent biologic advances have enabled Tregs to be genetically engineered to achieve tolerance and antigen-specific immune suppression by increasing their specific activity, stability and efficacy.[84] For instance, ganglioside D3 (GD3)-reactive chimeric antigen receptor Tregs have been developed for vitiligo treatment.[85] GD3-specific Tregs displayed increased immunosuppressive activity and significantly prevented depigmentation compared to untransduced Tregs in a T cell receptor transgenic mouse model of spontaneous vitiligo.[85]

Although adoptive transfer of antigen-specific Tregs provides a well-founded strategy to counteract aberrant autoimmunity in vitiligo, there remain unresolved concerns over its safety, specificity, long-term stability and the mechanisms underlying its effects at different timepoints and tissue locations. *In vivo* tracking will allow researchers to better understand the nature of antigen-specific Tregs. The combination of antigen-specific Tregs with either IL-2 or rapamycin might enhance Treg stability and clinical efficacy.[86]

Conclusions and future perspectives

This review has delved into the role of Tregs in vitiligo, emphasizing the feasibility of current therapeutic approaches targeting Tregs as a treatment modality (Figure 3). Ongoing experiments focusing on modulating the immune response of Tregs through immunological and signalling pathways signify a shift toward more precise and effective management of vitiligo.

It is noteworthy that therapeutic approaches targeting Tregs in vitiligo are challenging, as Tregs exhibit significant plasticity in the inflammatory microenvironment. Current endeavours primarily focus on enhancing Treg functionality and quantity through potential drug development, while also addressing metabolic alteration, post-translational modifications and interplay with other immune cells. Besides, given the uncertainty of the long-term efficacy and safety of Treg-based therapies, further clinical trials are warranted to guide clinical practice in this regard. Future explorations will pave the way for more tolerated, personalized and effective Treg-based therapeutics for patients with vitiligo.

Funding sources

This project received funding from the National Natural Science Foundation of China (grant/award number: 82073456 and 82173421); the Natural Science Foundation of Shanghai Municipality (grant/award number: 23ZR1408600); the Shanghai Sailing Program (grant/award number: 21YF1404400); and the Clinical Research Plan of SHDC (grant/award number: SHDC22022302).

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

Not applicable.

Patient consent

Not applicable.

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