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Regulatory T Cell Dysregulation in Vitiligo: A Meta-Analysis and Systematic Review of Immune Mechanisms and Therapeutic Perspectives

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ABSTRACT

Vitiligo is an autoimmune disorder marked by the progressive loss of skin melanocytes, increasingly linked to immune dysregulation as a key driver of disease onset and progression. Regulatory T (Treg) cells are essential for maintaining immune homeostasis by suppressing autoreactive immune responses. Mounting evidence implicates functional and numerical alterations in Treg cells in the pathogenesis of vitiligo. This study reviews findings on lesional and circulating Treg cells in vitiligo patients compared to healthy controls (HCs), examining Treg cell frequency, their ability to suppress $CD4^+$ and $CD8^+$ T cell activity, levels of the immunoregulatory cytokines interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), expression of the key suppressive marker FOXP3, as well as levels of the pro-inflammatory cytokines interleukin-17 (IL-17) and interleukin-22 (IL-22). A comprehensive systematic search was performed across Embase, MEDLINE/PubMed, and Scopus databases to identify eligible studies. A total of 21 studies comprising 1016 vitiligo patients and 846 HCs were included in the review. The analysis revealed a significant reduction in peripheral Treg cell counts ($p = 0.01$), impaired overall suppressive capacity of CD4+ and CD8+ T cells ($p = 0.01$), reduced levels of IL-10 ($p = 0.02$), increased levels of IL-17 ($p \leq 0.01$) and IL-22 ($p \leq 0.01$) in the blood of vitiligo patients compared to HCs. No statistically significant difference was observed in circulating TGF-β levels ($p = 0.1$). Most studies reported reduced FOXP3 expression in both skin and blood of vitiligo patients. Current evidence suggests vitiligo involves both reduced numbers and impaired function of Treg cells, supporting further study of Treg pathways as targets for immunomodulatory therapy.

1 | Introduction

Vitiligo is a chronic, autoimmune depigmenting disorder characterized by the selective destruction of epidermal melanocytes, primarily mediated by autoreactive $CD8^+$ T lymphocytes [1]. Affecting approximately 0.5–2% of the global population [2], the disease exhibits no significant predilection for sex, ethnicity, or geographic region [3]. Clinically, vitiligo manifests as well-demarcated, milky-white depigmented macules. During active phases, lesions may present with confetti-like depigmentation, trichrome patterns, or, less commonly, erythematous inflammatory borders. The term "non-segmental vitiligo" (NSV) encompasses all variants except the less prevalent segmental form [4]. NSV typically involves multiple, bilateral, and often symmetrical macules, with a clinical course characterized by alternating periods of lesion expansion and stability [1]. Disease recurrence is common, with relapse rates ranging from 40% to 70% within the first year post-treatment, often affecting the same anatomical sites [1, 3].

1.1 | Pathogenesis

Vitiligo pathogenesis is driven by a complex interplay of genetic and environmental factors. Genetic susceptibility largely involves variations in genes regulating immune function [5], such as polymorphisms in human leukocyte antigen (HLA) loci and Forkhead-box protein 3 (FOXP3) [3], as well as genes affecting melanocyte sensitivity to oxidative stress [2, 6]. Environmental triggers—including emotional stress [7], mechanical trauma [8], and ultraviolet radiation [9]—further contribute to disease onset and progression. Collectively, these factors initiate a cascade of autoimmune responses that ultimately result in the depletion of melanocytes [10–13].

1.2 | Treg Cells and Vitiligo

Regulatory T (Treg) cells, typically characterized as $CD4^+$ $CD25^+$ $FOXP3^+$ $CD127^{low}$ lymphocytes, play a pivotal role in maintaining immune tolerance by suppressing autoimmunity and limiting excessive effector T cell responses, such as those mediated by $CD4^+$ and $CD8^+$ T cells [7, 8, 14–26]. This immunoregulatory function is mediated, in part, through the secretion of anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) [27]. The transcription factor FOXP3 serves as a master regulator of Treg cell development and suppressive capabilities, and its expression is considered a defining and relatively unique feature distinguishing Treg cells from other T cell subsets [28].

In vitiligo, Treg cell plasticity toward proinflammatory T helper (Th) 1 [29–32] and Th17 [26, 29, 33] phenotypes has been observed, particularly within inflammatory microenvironments. Key mediators implicated in vitiligo pathogenesis include interferon-gamma (IFN-γ) and interleukin-15 (IL-15), both of which are associated with the Th1 immune response [31, 32, 34]. Furthermore, the pro-inflammatory cytokines interleukin-17 (IL-17) and interleukin-22 (IL-22), secreted by Th17 cells, have been implicated in disrupting the homeostatic balance between Th17 and Treg cells. This imbalance is thought to contribute to autoimmune destruction in vitiligo by sustaining chronic inflammatory responses [29].

The initial evidence implicating alterations in Treg cells in vitiligo pathogenesis arose from studies utilizing mouse models of immune-mediated melanoma control. Depletion of Treg cells not only enhanced tumor surveillance but also precipitated the onset of autoimmune skin depigmentation, providing a mechanistic link between Treg dysfunction and melanocyte loss [13, 35–37]. Since then, Treg cells have been a topic of research in vitiligo, and compelling evidence supports an autoimmune basis of the disease, with its pathogenesis involving alterations in the quantity and functionality of the Treg compartment [38]. Nonetheless, some investigations have yielded less definitive results, underscoring the heterogeneity and complexity of Treg involvement in vitiligo pathogenesis [39–42].

2 | Materials and Methods

2.1 | Search Strategy

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [43] (Table S1). The protocol was registered with the international Prospective Register of Systematic Reviews (PROSPERO CRD42024333236) [44], in accordance with PRISMA-P guidelines. Embase, MEDLINE/PubMed, and Scopus were searched from 1995 to November 2023 using the terms: "Regulatory T cell," "Tregs," "FOXP3" combined with "vitiligo". The search strategy is presented in Table S2.

2.2 | Eligibility Criteria

The inclusion criteria were: (1) participants of all ages, sexes, and ethnicities diagnosed with vitiligo; (2) case–control studies; (3) assessment of quantities of Treg cells and/or functions (specifically their suppressive capacity on CD4+ and CD8+ T-cells, immunosuppressive cytokines IL-10 and TGF-β and expression of FOXP3); (4) proper Treg cell definition by fluorescence-activated cell sorting (FACS) or equivalent methods; (5) studies published in English. Articles lacking outcomes of interest measured in terms of Treg cells in vitiligo were excluded.

2.3 | Data Selection Process

The titles and abstracts of all identified articles were compared against the inclusion criteria by two reviewers independently. Full texts were retrieved from articles that were considered eligible. As eligible articles were identified, reviewers screened the reference lists for additional relevant studies by backward citation searching. In case of any disagreements on study

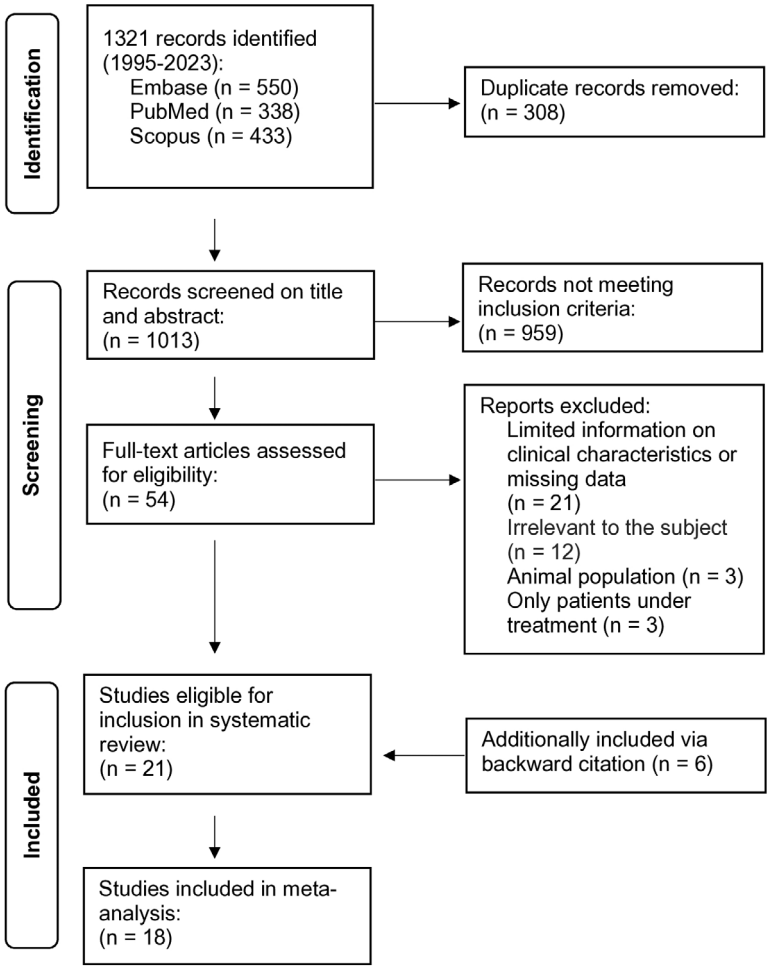

FIGURE 1 | The PRISMA flow chart depicts the study selection process. Initially, 1321 studies were identified through searches in Embase, MEDLINE/PubMed, and Scopus, and 308 duplicate articles were excluded. Following screening, 959 articles were removed as irrelevant. A total of 54 reports were requested for retrieval, and their full texts were evaluated for eligibility. Eligible studies were screened through backwards citation searching, resulting in the inclusion of six additional publications. Finally, 21 studies were included in this review, and 18 studies were assessed with meta-analysis.

eligibility, consensus was reached after discussion, involving the senior author if necessary. See Figure 1 for study selection process.

2.4 | Data Extraction

Two reviewers extracted data from the eligible articles using a predefined and piloted form. The main characteristics of each of the included studies are summarized in Table S3, including studied properties, number of cases and controls, clinical phase of vitiligo disease activity; stable (ST), active (A), definition of Treg cells by fluorescence-activated cell sorting (FACS) or other method, and outcomes. The data were synthesized using a meta-analysis as well as narrative synthesis when meta-analysis was not applicable. In case of missing data, attempts were made to contact the original authors.

2.5 | Risk of Bias and Quality Evaluation

Two reviewers independently assessed the risk of bias of the included studies using the Newcastle-Ottawa Scale (NOS) [45], resolving any differences in scoring through consensus after discussion. Detailed scores can be found in Table S4.

2.6 | Data Analysis and Synthesis

Meta-analyses were conducted using the R statistical software (Version 4.4.2) and heterogeneity was assessed by the Chi-square test and I^2 index. Means and standard deviations (SD) were collected from each studied value regarding Treg cells frequency and functionality in vitiligo patients and HC. For the bar plots in the figure, medians and ranges were extracted to calculate means and SDs using a standard approach. Forest plots were generated to illustrate the differences between the two groups (Figures 4, and 5 and Figures S12–S14). The pooled standardized mean difference (SMD) was estimated based on a random-effects meta-analysis model. Statistical significance was defined as $p < 0.05$ (two-sided).

2.7 | Publication Bias

The funnel plot method and Egger's regression were used to assess publication bias and heterogeneity (Figures S6–S11). As the

standardized mean difference (SMD) was used as an effect measure, two types of funnel plots are shown: one with the standard error and one with the inverse of the square root of the sample size on the y-axis [46].

2.8 | Meta-Regression

In situations where more than 10 studies were available in a meta-analysis, meta-regression were performed with the independent variable "proportion of active cases" (Figure 3).

2.9 | Sensitivity Analysis

Leave-one-out sensitivity analysis was applied to assess the influence of each study on the results (Figures S1–S5).

3 | Results

A total of 21 case–control studies, providing pooled information on 1016 vitiligo cases and 846 HC, contributed to this review. The completed PRISMA flow chart of the screening process is presented in Figure 1.

3.1 | Treg Cell Quantities in Blood

Meta-analysis was performed on 11 studies, which included 518 individuals with vitiligo and 437 HC, using random effect models. The results demonstrate significantly decreased Treg cell frequency in the blood of vitiligo patients compared to HC ($p=0.01$) with a SMD decrease in Treg cell frequency in vitiligo patients of −1.25 [95% confidence interval (CI) −2.22 to −0.28] (Figure 2).

To assess whether disease activity influenced the aforementioned results, a meta-regression analysis was performed using the proportion of active cases in each study as a moderator. The analysis did not reveal a significant association between disease activity and the standardized mean difference in Treg cell counts ($p=0.3193$) (Figure 3).

3.2 | Treg Cell Quantities in Skin

Four studies assessed Treg cell quantities in the skin of 74 vitiligo patients and 34 HC. We were not able to perform a meta-analysis due to heterogeneity in measurement methodologies. Two studies described reduced numbers of Treg cells in lesional, peri-lesional, and non-lesional skin of vitiligo patients compared to HC [47, 48]. One study reported unaltered quantities in lesional and non-lesional skin, but increased numbers in peri-lesional skin [38], and one study reported unaltered frequencies in non-lesional skin and increased frequencies in lesional and peri-lesional skin [39].

3.3 | Suppressive Capacity in Blood

Seven studies, comprising 241 vitiligo patients and 187 HC, assessed the suppressive capacity of Treg cells on CD4+ and CD8+ T-cells in blood and were evaluated through meta-analysis (Figure 4). Suppressive capacity was assessed by proliferation assays with co-culturing of effector and Treg cells and carboxyfluorescein succinimidyl Ester (CFSE) labeling using flow cytometry. Our analysis revealed significantly impaired overall Treg cells suppressive capacity on individuals with vitiligo cases compared to HC ($p=0.01$), SMD: −1.90 [95% CI −3.36 to −0.44]. Furthermore, subgroup analysis showed a significant reduction in Treg-mediated suppression of CD8+ T cells in vitiligo patients versus HCs ($p=0.01$), SMD: −2.42 [95% CI −4.38 to −0.46], whereas no significant impairment in the suppressive capacity of Tregs on the CD4+ T cells was found ($p=0.3$), SMD: −1.25 [95% CI −3.67 to −1.17].

3.4 | Immunosuppressive Cytokines in Blood

To further assess the suppressive capacity of Treg cells in vitiligo patients, levels of the immunosuppressive cytokines IL-10 and

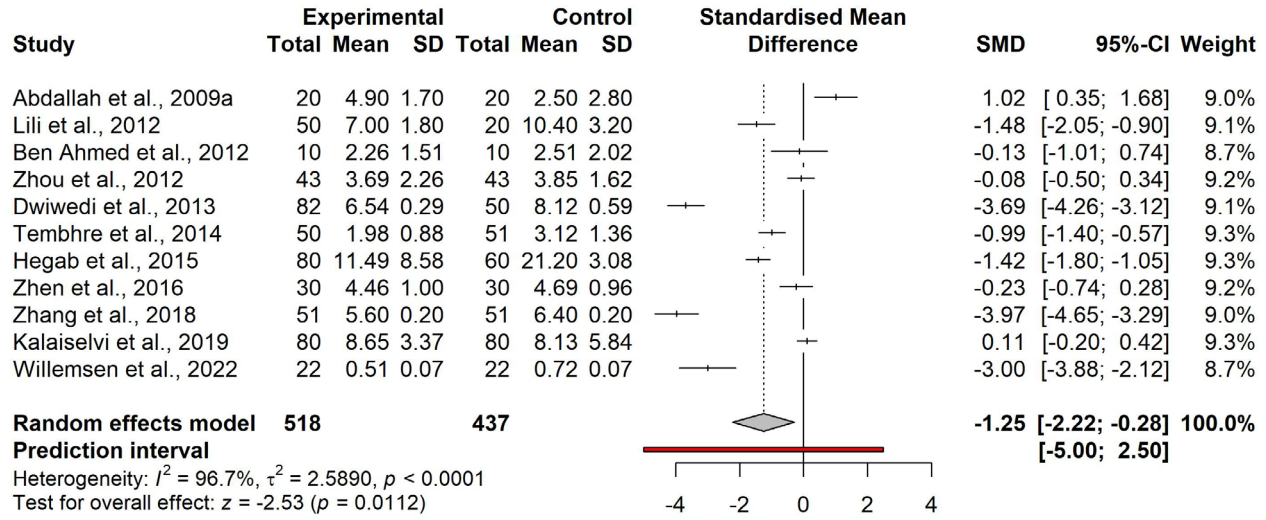

FIGURE 2 | Treg cells quantities in blood. The studies are sorted by the publication year. The diamond represents the summary estimate. The prediction interval gives the range in which a new study's effect estimate will fall.

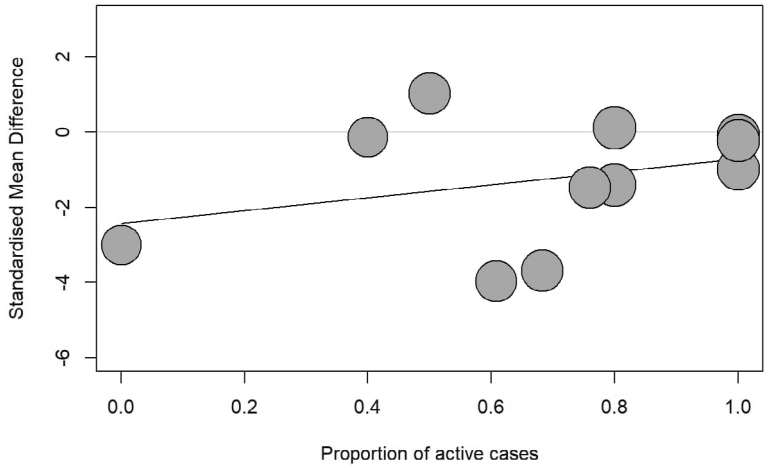

FIGURE 3 | Meta-regression analysis of the association between the proportion of active cases and effect size. Each bubble represents an individual study. The solid line depicts the meta-regression slope.

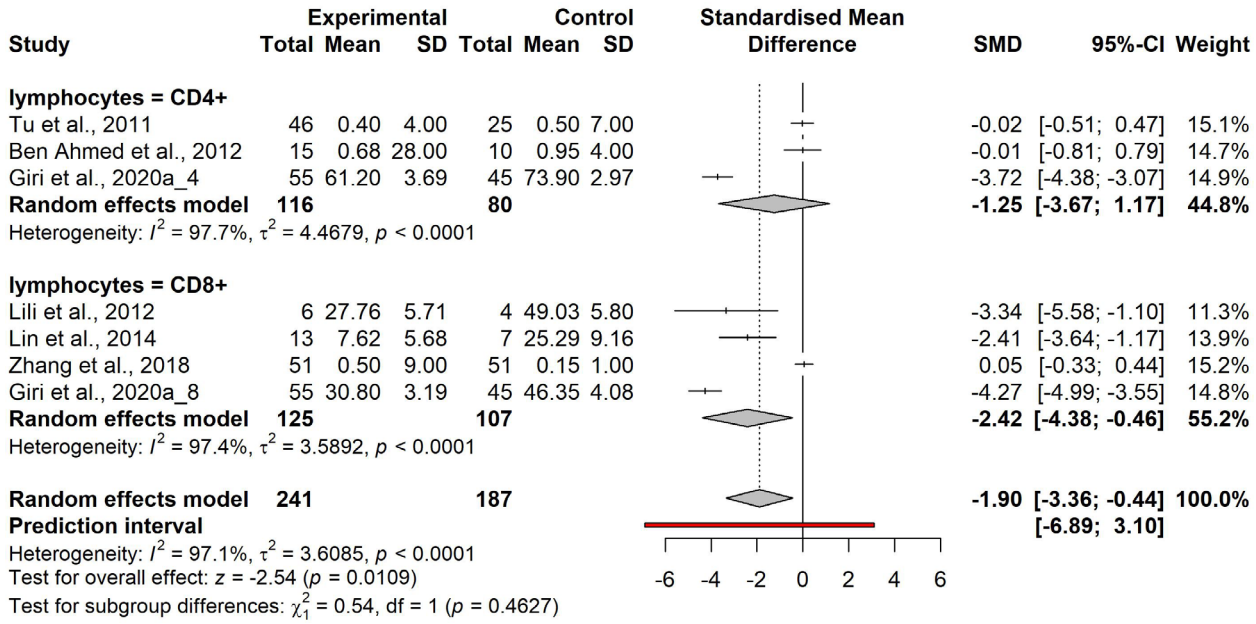

FIGURE 4 | Suppressive capacity of Treg cells on CD4+ and CD8+ T-cells in blood.

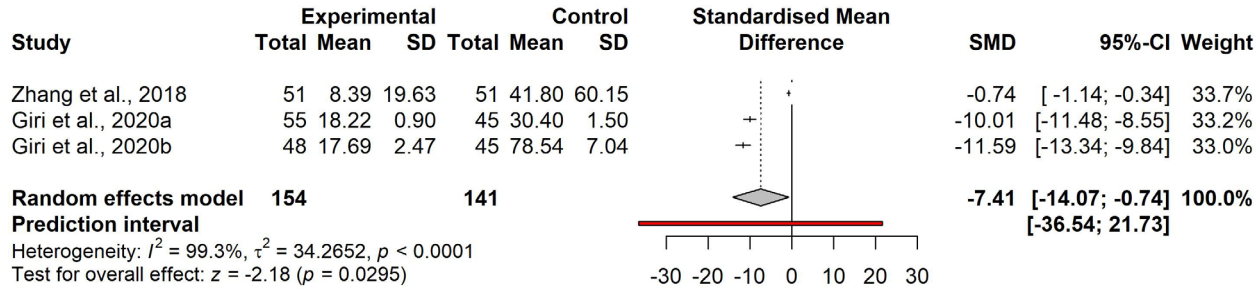

FIGURE 5 | Levels of IL-10 in blood.

TGF-β were assessed in blood by SMD. Three publications including 154 vitiligo patients and 141 HC were analyzed for IL-10 serum levels, showing a significant decrease in IL-10 serum levels in individuals with vitiligo compared to HC (p = 0.02), SMD: −7.41 [95% CI −14.07 to −0.74], Figure 5. Five studies for TGF-β serum levels were assessed, including 230 vitiligo patients and 196 HC. The results do not show significant alterations in TGF-β serum levels (p = 0.1), SMD: −2.75 [95% CI −6.10 to −0.59], Figure S12.

3.5 | Pro-Inflammatory Cytokines in Blood

Some studies also reported pro-inflammatory cytokine levels, which, though not directly linked to vitiligo in current understanding, are included for methodological completeness in the systematic review and meta-analysis. Three studies, including 133 vitiligo patients and 140 HC, and two studies, including 103 vitiligo patients and 110 HC were evaluated for the levels of the Th17-related pro-inflammatory cytokines IL-17 and IL-22 in blood, respectively. Meta-analysis demonstrated significantly increased cytokine levels in vitiligo patients compared to HC; IL-17: ($p \leq 0.01$), SMD: 3.43 [1.31–5.56], Figure S13; IL-22: ($p \leq 0.01$), SMD: 6.35 [0.89–11.81], Figure S14.

3.6 | Transcription Factors

Due to the heterogeneity in measurement units and reporting formats across these studies, a meta-analysis could not be performed.

3.6.1 | FOXP3 Levels in Blood

FOXP3 expression in Treg cells peripheral blood mononuclear cells (PBMCs) was evaluated by FACS in multiple studies and by polymerase chain reaction (PCR) in one study. Among these, six reported a significant reduction in FOXP3 expression in Treg cells of vitiligo patients compared to HCs [49–54], although two publications reported unaltered [55, 56] and one study increased [57] levels.

3.6.2 | FOXP3 Levels in Skin

FOXP3 protein expression in skin was assessed by immunohistochemistry (IHC), while mRNA levels were measured using PCR. Most studies reported a decrease in FOXP3 expression in lesional skin [49, 58–60] and one study on the other hand reported increased FOXP3 expression in the lesional skin of vitiligo patients [39].

4 | Discussion

Our meta-analysis demonstrated significantly decreased Treg cell count in the blood and skin of vitiligo patients compared to HCs. Multiple mechanistic pathways may contribute to reduced Treg frequency, including pro-inflammatory cytokine-induced apoptosis [21], impaired migration due to altered chemokine gradients, and defective differentiation associated with FOXP3 or microRNA dysregulation [61]. While currently no approved therapy specifically and solely increases Tregs in vitiligo, research is ongoing on advanced Treg-targeted therapeutics, such as low-dose interleukin 2 (IL-2) or metabolic and signaling pathway modulators [62, 63]. Additionally, monoclonal antibodies targeting Treg cell surface markers or immune checkpoint molecules—therapies with established efficacy in other autoimmune diseases—are emerging as promising strategies to selectively modulate Treg function or trafficking in vitiligo. Other novel approaches include the depletion of T resident memory cells by an IL-15Rβ antibody [24]. However, these agents remain in the preclinical stage or are being evaluated in early-phase clinical trials [64].

4.1 | Treg Cell Quantities in Blood

In blood, Treg cell counts were significantly decreased in vitiligo patients compared to HCs. Some studies reported that lower Treg numbers correlated with earlier disease onset [50], greater severity [51], and increased CD8+ T cell activity [38].

4.2 | Treg Cell Quantities in Skin

Among the included studies, data remain inconsistent, with some studies suggesting increased or unaltered Treg levels [38, 39, 65]. However, most studies examining both lesional and perilesional skin in vitiligo patients demonstrate a reduction in skin-resident Treg cells [47, 48]. Interestingly, the abundance of Tregs positively correlates with the number of CD8+ T cells in perilesional skin [38], suggesting an active Treg cell recruitment to sites of inflammation to counterbalance the immune response. However, it is thought that deficient Treg numbers remain insufficient to fully suppress the autoreactive CD8+ T cells. JAK inhibitors represent a novel and promising topical therapy for vitiligo by reducing pathogenic T cell activity and inflammation, potentially creating a more favorable environment for Tregs to function effectively. As of June 2025, topical ruxolitinib, a JAK inhibitor, is the only therapy approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Swissmedic for therapy-refractory vitiligo [66]. Other topical formulations such as topical calcineurin inhibitors and topical steroids are commonly used but have not received regulatory approval for the treatment of vitiligo yet [67].

4.3 | Suppressive Capacity of Treg Cells on CD4+ and CD8+ T-Cells in Blood

Beyond numerical alterations in Treg cells, it is crucial to assess their functional suppressive capacity, as this may play an even more significant role in immune regulation and disease pathogenesis. Our analysis revealed a significant decrease in the overall Treg cells' suppressive capacity of effector T cells, especially for $CD8^+$ T cells in vitiligo patients. The expansion of CD8+ T cells with a concomitant decrease in Tregs was significantly higher in patients with active compared to stable disease status [50]. Notably, suppression of $CD4^+$ T cells was not significantly altered in our analysis, despite reports from other studies indicating diminished regulatory function linked to disease activity [39, 51] and severity [52]. Cumulatively, substantial in vitro evidence supports the notion of impaired Treg-mediated suppression in the peripheral blood of vitiligo patients. However, whether these functional alterations accurately reflect the immunoregulatory landscape in skin remains unclear.

4.3.1 | Levels of Suppressive Cytokines in Blood

Treg cells secrete IL-10 and other cytokines such as TGF-β for their immunosuppressive function. Our meta-analysis showed

decreased expression in blood of IL-10, both at protein and mRNA levels within circulating Treg cells, but TGF-β levels were not significantly altered, although a trend toward reduction was observed (SMD: −2.75). This might be explained by a high variability of clinical phenotypes assessed in different studies but also due to missing investigation and comparison to tissue TGF-β levels in the respective studies. Data on novel IL-10-based approaches, including recombinant IL-10 administration, have shown that increasing IL-10 levels can lead to improved outcomes in terms of repigmentation and disease activity, as inducing Treg cells [68, 69]. However, IL-10–based therapies for vitiligo remain investigational, with current evidence largely limited to preclinical studies and early-stage research, underscoring the need for further clinical evaluation. One clinical study has explored combination treatments that increase TGF-β levels indirectly—which showed improved outcomes in vitiligo patients [70]. However, these are not yet established or approved therapies.

4.4 | Pro-Inflammatory Cytokines in Blood

The Th17-associated cytokines IL-17 and IL-22 were reported to be significantly elevated in the blood of vitiligo patients compared to HCs. This could suggest a skewing of the balance of Th17/Treg toward inflammation. Based on these findings, targeting IL-17 or IL-22 could be a reasonable hypothesis. A clinical study using the IL-17 inhibitor secukinumab was prematurely interrupted due to worsening of vitiligo in 7 of 8 included patients [71]. The current understanding is that elevation of IL-17 is not directly associated with disease pathogenesis [69]. IL-22 remains a potential therapeutic target due to its role in keratinocyte-induced melanocyte apoptosis [72] but to date, no clinical studies are actively investigating therapeutic strategies that target this pathway.

4.5 | FOXP3 Levels in Blood

FOXP3 expression is consistently found to be reduced in the blood Treg cells of vitiligo patients, redundant with lower Treg cell numbers. This impaired FOXP3 expression has been associated with certain genetic polymorphisms that confer increased susceptibility to vitiligo [73–75]. Systemic approaches inducing Treg cells, which also include enhancing regulatory factors such as FOXP3 or suppressive markers such as CTLA-4, such as low-dose IL-2 therapy [62] and histone deacetylase (HDAC) inhibitors, are currently under experimental evaluation, though they remain at preliminary stages [76].

4.6 | FOXP3 Levels in Skin

FOXP3 expression is generally reduced in the skin of vitiligo patients, particularly in lesional areas, signaling a key failure in immune regulation. Interestingly, one study reported a relative increase of FOXP3 in lesional skin [39]. This variability may depend on disease stage; during active phases, heightened local immune activity can elevate FOXP3 levels. However, elevated FOXP3 in lesional skin does not necessarily reflect increased or fully functional Treg populations, suggesting the immune regulation remains impaired [77]. Therapeutic approaches, including small molecules that upregulate FOXP3 expression, Treg cell inducing therapies such as low-dose IL-2 and adoptive transfer of regulatory T cells, hold significant potential for restoring immune homeostasis in vitiligo. However, these interventions remain predominantly experimental and necessitate comprehensive mechanistic validation before clinical translation can be realized [78, 79].

5 | Study Limitations

The primary limitation of this meta-analysis was the substantial heterogeneity observed across the included studies. This variability is partly attributable to differences in the clinical phenotypes evaluated in each publication, reflecting the complex nature of Treg cell characteristics in vitiligo, which are influenced by factors such as disease onset, activity, and severity. Methodological factors like inconsistent blood or biopsy sampling protocols can alter lymphocyte quantification [80]. Concurrent pathological states, such as chronic infections, may further perturb Treg/CD8+ T cell ratios [81]. Additional factors, such as genetic or environmental influences, may also introduce heterogeneity, thereby affecting the comparability of results. While many investigations implemented matched controls, insufficient sample sizes and disproportional case–control ratios limit statistical power to adjust for covariables. To face study-level heterogeneity, a random-effects model was used in the meta-analysis to address differences between studies. Subgroup analyses focusing on Treg cell effects on CD4+ and CD8+ T-cells were performed to better understand their specific roles. Meta-regression analysis was conducted to assess disease activity as a source of heterogeneity, revealing that it does not explain observed variability in Treg cell counts in blood. Also, sensitivity analyses were carried out to test the reliability of results under different study criteria and methods. Our search strategy limited eligible studies for systematic review on the cytokines IFN-γ and IL-15, playing important roles in the Treg cell induction [29, 41, 68, 82] and vitiligo maintenance [16, 31, 83], respectively.

6 | Conclusion

Taken together, a quantitative reduction and functional impairments of Treg cells emerge as a core immunopathological feature in vitiligo patients. A better understanding of the role of Treg cells in vitiligo pathogenesis will pave the way for the development of innovative and targeted therapeutic strategies to effectively treat patients with this condition. Some results, however, remain elusive and variable across studies. Therefore, larger studies are needed to understand the complex functional network of Treg cells in vitiligo pathogenesis.

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Conflicts of Interest

T.P. is a consultant for AbbVie, Almirall, Amgen, Bristol Myers Squibb, Calypso, Galderma, Incyte Corporation, Janssen, Eli Lilly, Novartis, Pfizer, Roivant, UCB, and VYNE Therapeutics. He has received grants and/or honoraria from AbbVie, ACM Pharma, Almirall, Amgen, Astellas, Bristol Myers Squibb, Calypso, Celgene, Galderma, Genzyme/Sanofi, GlaxoSmithKline, Incyte Corporation, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Roivant, Sun Pharmaceuticals, UCB, and VYNE Therapeutics. He is the cofounder of YUKIN Therapeutics; and has patents on WNT agonists or GSK3b antagonist for repigmentation of vitiligo and the use of CXCR3B blockers in vitiligo. The other authors declare no conflicts of interest related to this work.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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