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ORIGINAL ARTICLE

Repigmentation in vitiligo using janus kinase (JAK) inhibitors with phototherapy: systematic review and Meta-analysis

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ABSTRACT

Introduction: Vitiligo is an autoimmune disorder characterized by progressive loss of melanocytes, leading to cutaneous depigmentation. Vitiligo has significant psychosocial impacts on patients and is challenging to manage with limited treatment options. Recent studies have suggested promising results for JAK1/3 inhibitors including tofacitinib and ruxolitinib.

Objective: To determine the expected response of vitiligo to JAK inhibitor therapy and factors which influence response rates.

Methods: A systematic review and meta-analysis was performed according to PRISMA guidelines. Good response was defined as repigmentation >50% or a 'good' or 'excellent' outcome as described by authors. Partial response was defined as some repigmentation <50%.

Results: From the 9 eligible studies, individual patient data from 45 cases were pooled. Good response was achieved in 57.8%, partial response in 22.2%, and none or minimal response in 20% of cases. When subgrouped according to site, facial vitiligo had the highest good response rate (70%), compared to extremities (27.3%) and torso/non-sun exposed areas (13.6%). Concurrent phototherapy was significant associated with higher rates of good overall response ($p < .001$) and good facial response ($p < .001$).

Conclusions: There is promising low-quality evidence regarding the effectiveness of JAK inhibitors in vitiligo. Concurrent UVB phototherapy appears to improve efficacy of JAK inhibitors for vitiligo.

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KEYWORDS
vilitigo; JAK inhibitors; Janus kinase

Introduction

Vitiligo is an autoimmune disorder characterized by progressive loss of melanocytes, leading to cutaneous depigmentation. Vitiligo has significant psychosocial impacts on patients and is challenging to manage with limited treatment options (1,2). Treatment options include topical corticosteroids, topical calcineurin inhibitors and narrow band ultraviolet B (UVB)as monotherapy or in combination. Re-pigmentation rates and efficacy of current traditional treatment options have been variable, and incomplete or non-response to treatment is common (3–6).

Recent studies have suggested promising results for JAK1/3 inhibitors including tofacitinib and ruxolitinib (7,8). The majority of the literature to date is based on small volume data, with a lack of definitive evidence or guidelines. To address these current gaps in knowledge, we performed a systematic review and meta-analysis of available individual patient data from case reports, series and trials.

Methods

Search strategy

The present study was performed according to PRISMA guidelines. Electronic searches were performed using Ovid Medline, PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to November 2019. To achieve the maximum sensitivity of the search strategy, we combined the terms: 'vitiligo' and 'Janus Kinase' or 'JAK inhibitor' or 'ruxolitinib or tofacitinib or baracitinib' as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies, assessed using the inclusion and exclusion criteria.

Selection criteria

Eligible studies for the present systematic review and meta-analysis included those in which patient from case reports, case series, cohort studies, or clinical trials with vitiligo were treated with JAK inhibitor therapy. Studies that did not report response or complications as endpoints were excluded. All publications were limited to those involving human subjects. Language was not an exclusion factor. Abstracts, conference presentations, editorials, reviews and expert opinions were excluded. The search strategy is included in Supplementary Table 1.

Data extraction

All data were extracted from article texts, tables and figures. Two investigators independently reviewed each retrieved article (K.P, S.P.). Discrepancies between the two reviewers were

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Supplemental data for this article can be accessed here.

resolved by discussion and consensus. Individual patient level data extracted from case reports/case series/clinical trials were pooled together as 'individual cases' group. Clinical trials and cohort studies reporting descriptive statistics of cohort-level data were also included. Good response was defined as repigmentation >50% or a 'good' or 'excellent' outcome as described by authors. Partial response was defined as some repigmentation <50%.

Statistical analysis

For individual patient level data, the data was analyzed using descriptive statistics. Univariate analysis was performed according to factors: no phototherapy vs phototherapy, oral vs topical JAK inhibitor therapy. All analyses were performed using the metafor package for R version 3.4 or SPSS version 24. p values <.05 were considered statistically significant.

Results

A total of 136 studies were identified through six electronic database searches and from other sources such as reference lists (Supplementary Figure 1). After exclusion of duplicate or irrelevant references, **32** potentially relevant articles were retrieved. There were some studies with overlapping populations that were removed. After detailed evaluation of these articles, a total of 9 articles were included in the present study, comprising individual patient data from 45 cases.

Summary characteristics of the pooled individual cases from case reports/series is summarized in Table 1. The mean age was 47 years, with 52.8% males. Oral therapy was used in 55.6% cases whereas topical therapy was used in 44.4% cases. Concurrent UVB phototherapy was used in 60% of cases.

Efficacy of JAK inhibitors for vitiligo

Overall, good response was achieved in 57.8%, partial response in 22.2%, and none or minimal response in 20% of cases. When subgrouped according to site, facial vitiligo had the highest good response rate (70%), compared to extremities (27.3%) and torso/non-sun exposed areas (13.6%) (Table 2).

Effect of concurrent phototherapy on JAK inhibitor efficacy

The proportion of good response in patients who received JAK inhibitors alone was significantly lower compared to who received concurrent phototherapy (11.1% vs 88.9%, $p < .001$) (Table 3). When subgrouped according to body site, this difference was more noted in facial vitiligo (26.7% vs 94.4%, $p < .001$), but not as marked for extremities (13.3% vs 57.1%, $p = .083$) or torso and non-exposed areas (6.7% vs 40%, $p = .283$).

Effect of route of JAK inhibitors

There was no difference in good response rates in patients taking oral vs topical forms of JAK inhibitors for vitiligo (44% vs 75%, $p = 0.1$) (Table 4). Subgroup analysis did not show significant difference in good response rates in the face (46.1% vs 75%, $p = .229$), extremities (21.4% vs 37.5%, $p = .329$), or torso/non-sun exposed sites (7.1% vs 25%, $p = .31$).

Safety of JAK inhibitors for vitiligo

Complications are summarized in Table 1. These included erythema (11/45, 24.4%), transient acne (4/45, 8.9%), hyperpigmentation (9/45, 20%), transient increased in lipids (4/45, 8.9%), upper respiratory tract infection (2/45, 4.4%), weight gain (1/45, 2.2%) and arthralgia (1/45, 2.2%). There were no subjects who developed new malignancies or tuberculosis reactivation. No subjects required hospitalization for JAK inhibitor related adverse events.

Discussion

There is an increasing amount of literature supporting the use of JAK 1/3 inhibitors in a number of conditions, including rheumatoid arthritis atopic eczema (Ref), and plaque psoriasis (9,10). These is also evidence showing some efficacy in alopecia areata (11). Given shared similarities in genetic risk factors between alopecia areata and vitiligo, it has been suggested there may be some common pathways involved in their underlying pathogenesis (12). Vitiligo involves the destruction of melanocytes *via* cell-mediated immunity, of which interferon-gamma and CD8+ T cells are key players (13,14). Alopecia areata is also similarly driven by a CD8+ T cell autoimmune process (15), which suggests targeted therapies may be efficacious in both conditions. Clinically too, some patients are noted to have both diseases concurrently or successively. As such, it may be plausible to consider a medication that has efficacy in alopecia areata for possible therapy in vitiligo.

By pooling individual patient level data from case reports, case series and clinical trials, we were able to perform univariate analysis to assess factors which contribute to response to JAK inhibitor therapy. Overall, our analysis shows some promise for this class of medications for vitiligo.

Specifically, we found that a good response or repigmentation rate >50% was found in 57.8% of cases. When used concurrently with phototherapy, the good response rate improved to 88.9% for those using JAK inhibitors and phototherapy. This observation has been previously reported, although underlying mechanisms remain unclear. It has been suggested that combined treatment with UV-B therapy aids re-pigmentation by causing immunosuppression and simulating melanocytes (16,17). Photoactivation of melanocytes allow them to leave their stem cell niche and seed the epidermis to make pigment whilst the JAK inhibitor suppresses the autoimmune CD8+ and interferon-gamma dependent responses (17) which attack melanocytes and cause depigmentation otherwise. In keeping with this, indeed improved responses to JAK inhibitors in sun-exposed areas has been documented (18).

Our analysis did not demonstrate any significant differences in oral vs topical route of JAK inhibitors. We found an overall low complication rate. The most common side effects were transient and included erythema and acne. There were no cases of new malignancies or reactivation of tuberculosis, although we note that follow-up for available published cases is limited and still ongoing. Laboratory changes were minimal, and most common were mild lipid abnormalities. As complication rates were low, we did not find any significant difference in complication profiles between oral versus topical JAK inhibitors, although intuitively topical agents would be of lower risk. There is more abundant evidence in rheumatology and rheumatoid arthritis in terms of adverse effect risk profile for JAK inhibitors. There have

Table 1. Characteristics of included studies.

Author	Year	Number of patients	Mean Age (years)	Treatment	Duration (wks)	Area affected	Outcome	Side effects
Craiglow	2015	1	50	PO tofacitinib 5mg every 2 days, then OD	20	Forehead, trunk, extremities	Complete repigmentation of forehead/ hands, partial repigmentation of other areas. Overall pigmentation improved from 10% to 95%	Nil
Gianfaldoni	2018	9	NA	PO tofacitinib 5mg BD + UVB phototherapy	NA	NA	All 9 patients achieved nearly complete repigmentation, with overall rate pigment improvement of 92%	Nil
Harris	2016	1	35	PO ruxolitinib 20mg BD	20	Face, trunk, extremities	Significant improvement in facial pigmentation from 0.8% to 51%	Nil adverse effects. 12 weeks after treatment was stopped, regained pigment had regressed
Josahipura (case reports)	2018	2	49	TOP ruxolitinib 1.5% cream BD	38	Face	Improvement in sun-exposed areas only	Nil
Josahipura (open label extension, extention of Rothstein)	2018	8	50 (33–62)	TOP ruxolitinib 1.5% cream BD + UVB phototherapy	12	Facial, upper limbs, acral, trunk	5 of 8 patients had a treatment response. 4 patients with facial vitiligo had mean 92% improvement in pigmentation at 52 weeks. 3 of 6 patients had response in non-acral upper extremities (12.6% improvement), slight acral repigmentation seen in 1 patient. 2 of 3 patients responded on the trunk (16.7% improvement)	Erythema in 3 of 8 patients, transient acne in 2 patients
Kim	2018	2	30	PO tofacitinib 5mg BD + UVB phototherapy	12	Face, neck, chest, forearms, shins, hands	Facial repigmentation was near complete for 1 case and 75% for case 2. Repigmentation of other body sites only occurred for one case	Nil
Liu	2017	10	54	PO tofacitinib 5–10mg daily-BD	40	Face, torso, arms, hands, legs, feet	5 of 10 patients achieved some repigmentation, only in sun-exposed areas of skin in 3 of them, and in 2 other cases who had UVB phototherapy. Overall mean decrease 5.4% BSA involvement with vitiligo	Weight gain in 1 patient, arthralgia in 1 patient, mild increase in lipids in 4 patients. Recurrence after discontinuation of therapy, repigmentation achieved when restarted JAKinhibitor. Repigmentation when therapy restarted
Mckesey	2019	11	44	TOP tofacitinib 2% BD cream + UVB phototherapy	12	Facial	Good-excellent repigmentation in all patients. Mean improvement in fVASI of 70%	Nil
Vu	2017	1	44	PO tofacitinib 5mg BD	24	Multifocal	Marginal decrease in VASI score from 4.68 to 3.95	2 episodes of self-resolving upper respiratory tract infection and diarrhea
Rothstein (excluded from analysis, follow-up study published by Josahipura et al 2018)	2017	11	52 (33–65)	TOP ruxolitinib 1.5% cream BD	20	Facial, upper limbs, acral, trunk	4 patients had facial involvement, 76% improvement in fVASI at week 20. A 23% improvement in overall VASI was observed in all enrolled patients. 3 of 8 patients responded on body surfaces, 1 of 8 patients responded on acral surfaces.	8 of 11 patients had erythema. Rim of hyperpigmentation around patches seen in 9 of 11 patients. Transient acne seen in 2 patients

Table 2. Summary demographics and outcomes in included studies.

Age (mean ± SD)	47 ± 9.0 years
Sex	
Male	19 (52.8%)
Female	17 (47.2%)
Route of JAK inhibitor	
Oral	25 (55.6%)
Topical	20 (44.4%)
Concurrent UVB phototherapy	
Yes	27 (60%)
No	18 (40%)
Duration of therapy (weeks)	21.2 ± 15
Overall response	
Good	26 (57.8%)
Partial	10 (22.2%)
None/marginal	9 (20%)
Facial response	
Good	21 (70%)
Partial	3 (10%)
None/marginal	6 (20%)
Extremities response	
Good	6 (27.3%)
Partial	3 (13.6%)
None/marginal	13 (59.1%)
Torso/non-sun exposed areas response	
Good	3 (13.6%)
Partial	2 (9.1%)
None/marginal	17 (77.3%)

Table 3. Association between concurrent UVB-phototherapy and JAK inhibitor response.

	No phototherapy	Phototherapy	*p*-value
Overall response			
Good	2 (11.1%)	24 (88.9%)	<.001
Partial	7 (38.9%)	3 (11.1%)	
None/marginal	9 (50%)	0	
Facial response			
Good	4 (26.7%)	17 (94.4%)	<.001
Partial	2 (13.3%)	1 (5.6%)	
None/marginal	9 (60%)	0	
Extremities response			
Good	2 (13.3%)	4 (57.1%)	.083
Partial	2 (13.3%)	1 (14.3%)	
None/marginal	11 (73.3%)	2 (28.6%)	
Torso/non-sun exposed areas response			
Good	1 (6.7%)	2 (40%)	.283
Partial	1 (6.7%)	1 (20%)	
None/marginal	13 (86.7%)	2 (40%)	

Table 4. Association between route of JAK inhibitor therapy and response.

	Oral	Topical	*p*-Value
Overall response			
Good	11 (44%)	15 (75%)	.1
Partial	8 (32%)	2 (10%)	
None/marginal	6 (24%)	3 (15%)	
Facial response			
Good	6 (46.1%)	15 (75%)	.229
Partial	2 (15.4%)	1 (5%)	
None/marginal	5 (38.5%)	4 (20%)	
Extremities response			
Good	3 (21.4%)	3 (37.5%)	.329
Partial	3 (21.4%)	0	
None/marginal	8 (57.2%)	5 (62.5%)	
Torso/non-sun exposed areas response			
Good	1 (7.1%)	2 (25%)	.31
Partial	2 (14.3%)	0	
None/marginal	11 (78.6%)	6 (75%)	

been reports of possible associations with herpes zoster infections (19), tuberculosis reactivation (20), and gastrointestinal perforation (21). It is important to emphasis for clinicians using JAK inhibitors that the possibility of serious and lethal adverse effects is plausible, and that safety profile data for this class of agents in vitiligo is still in its infancy.

This study has several limitations. This meta-analysis was based on available low-quality evidence, predominantly in the form of case reports, which require confirmation in large randomized trials and follow-up. Observer bias will be significant as a result of clinician and study participants being unblinded. There is also significant selection bias and publication bias, given that it is likely that only positive results are published. We acknowledge that a meta-analysis of clinical cases does not replace the degree of evidence provided by randomized clinical trials, however, it does serve as a hypothesis generator to explore some clinical questions regarding the use of JAK inhibitors in vitiligo.

Conclusion

There is some promising preliminary data for the treatment of vitiligo with JAK inhibitors. Light-exposure or concurrent UVB phototherapy appears to improve efficacy of JAK inhibitors for vitiligo. Future large-sized randomized studies are required to confirm these findings.

Ethics approval

Not required as this is a systematic review.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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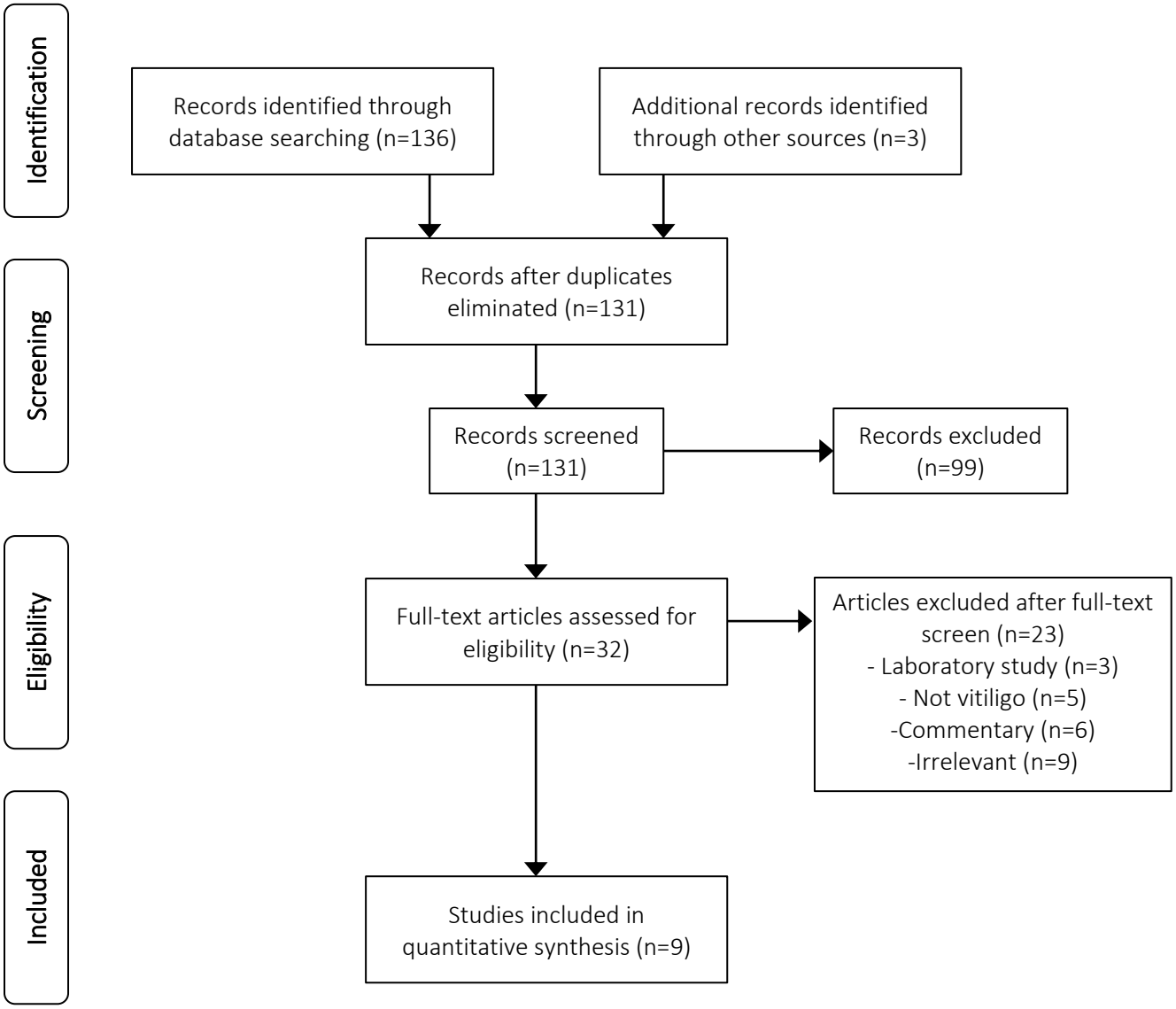
Identification
Screening
Eligibility
Included
Records identified through database searching (n=136)
Additional records identified through other sources (n=3)
Records after duplicates eliminated (n=131)
Records screened (n=131)
Records excluded (n=99)
Full-text articles assessed for eligibility (n=32)
Articles excluded after full-text screen (n=23)
- Laboratory study (n=3)
- Not vitiligo (n=5)
-Commentary (n=6)
-Irrelevant (n=9)
Studies included in quantitative synthesis (n=9)

Supplementary Table 1. Search strategy

Number	Search strategy	Results
1	vitiligo.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq]	23237
2	Janus Kinase.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq]	43557
3	JAK inhibitor.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq]	3796
4	ruxolitinib.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq]	6159
5	tofacitinib.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq]	6336
6	baracitinib.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, dq]	23
7	1 and (2 or 3 or 4 or 5 or 6)	136