Title: Efficacy and safety of JAK inhibitors in the management of vitiligo: a systematic review and meta-analysis

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Supplementary material

Efficacy and safety of JAK inhibitors in the management of vitiligo: a systematic review and meta-analysis

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Methods

The study followed the recommendations outlined in the Cochrane Handbook (1) and the results were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (2). The study protocol was registered in the PROSPERO database under registration number CRD42023445503.

Eligibility criteria

Eligible studies were assessed using the Population, Intervention, Control, Outcome (PICO) format as follows: P- Patients with vitiligo, I- JAKi administered topically or orally, C- Placebo, vehicle cream, or conventional therapy, and O- Percentage change from baseline; patients who achieved a 75% improvement in their facial Vitiligo Area Scoring Index (VASI) score or total VASI score, as well as adverse events.

Information sources

The systematic search was conducted from inception through September 10, 2023, across three databases (Medline, EMBASE, Cochrane) without language restrictions or filtering options. The search key included two domains: JAK inhibitors and vitiligo.

Search strategy

Database searched	**via**	**Records**
MEDLINE	PubMed	143
Embase	Embase.com	396
Cochrane Library	Cochranelibrary.com	65
Total		**604**

Table S1. Number of hits in the electronic databases.

Search key for systematic search used in each electronic database:

PubMed: (janus kinase inhibitor OR jak inhibitor OR jak1 inhibitor OR jak2 inhibitor OR jak3 inhibitor OR ruxolitinib OR tofacitinib OR baricitinib OR oclacitinib OR upadacitinib OR itacitinib OR filgotinib OR abrocitinib OR povorcitinib OR deucravacitinib OR ritlecitinib OR brepocitinib OR gusacitinib OR delgocitinib OR solcitinib OR ifidancitinib OR cerdulatinib) AND (vitiligo)

EMBASE: (janus kinase inhibitor/exp OR janus kinase inhibitor OR jak inhibitor/exp OR jak inhibitor OR jak1 inhibitor/exp OR jak1 inhibitor OR jak2 inhibitor/exp OR jak2 inhibitor OR jak3 inhibitor/exp OR jak3 inhibitor OR ruxolitinib/exp OR ruxolitinib OR tofacitinib/exp OR tofacitinib OR baricitinib/exp OR baricitinib OR oclacitinib/exp OR oclacitinib OR upadacitinib/exp OR upadacitinib OR itacitinib/exp OR itacitinib OR filgotinib/exp OR filgotinib OR abrocitinib/exp OR abrocitinib OR povorcitinib/exp OR povorcitinib OR deucravacitinib/exp OR deucravacitinib OR ritlecitinib/exp OR ritlecitinib OR brepocitinib/exp OR brepocitinib OR gusacitinib/exp OR gusacitinib OR delgocitinib/exp OR delgocitinib OR solcitinib/exp OR solcitinib OR ifidancitinib/exp OR ifidancitinib OR cerdulatinib/exp OR cerdulatinib) AND (vitiligo/exp OR vitiligo)

Cochrane Library: (janus kinase inhibitor OR jak inhibitor OR jak1 inhibitor OR jak2 inhibitor OR jak3 inhibitor OR ruxolitinib OR tofacitinib OR baricitinib OR oclacitinib OR upadacitinib OR itacitinib OR filgotinib OR abrocitinib OR povorcitinib OR deucravacitinib OR ritlecitinib OR brepocitinib OR gusacitinib OR delgocitinib OR solcitinib OR ifidancitinib OR cerdulatinib) AND (vitiligo)

Advanced search was used in Embase and CENTRAL. No additional filter or setting was used.

Date of search: 22 October 2023

Selection process

Search results were exported to the EndNote 20 citation manager (Clarivate Analytics, Philadelphia, PA, USA). After automatic and manual duplicate removal (AAM), articles were selected using the Rayyan Intelligent Systematic Review program. Two independent review authors (AAM, IS) performed the selection based on title, abstract, and full text, following the inclusion criteria. Disagreements were resolved by a third reviewer (ASL), and Cohen's Kappa coefficient was calculated at each selection step to evaluate the level of agreement.

Data collection process

Data from eligible articles were collected independently by three reviewers (AM, IS, DP) using a predesigned sheet. Disagreements were resolved by a fourth (ASL) reviewer.

Data items

The following data were extracted: first author, year of publication, study population, study period, population characteristics, assigned intervention and control treatment and all outcome parameters (%CFB, F-VASI75, T-VASI75, AEs).

Study risk of bias assessment

Two authors (AAM, IS) independently conducted a risk-of-bias assessment using the Cochrane risk-of-bias tool for randomised trials (RoB-2) and Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I). The evaluation involved categorising each study outcome as "low," "some concerns", or "high" risk of bias. Disagreements were resolved by a third reviewer (ASL). The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) software tool (GRADEPro) was used to assess the certainty of evidence for outcome parameters of the primary analysis (3).

Synthesis methods

A minimum of three studies were required for the meta-analysis. Given the anticipated heterogeneity, a random-effects model was employed. Effect sizes, including proportions and Risk Ratios (RR) with 95% confidence intervals (CI), were calculated. Both proportions and RRs were derived from patient and event numbers in the individual studies. Pooled proportions were estimated using a random intercept logistic regression model as recommended by Schwarzer et al. and Stijnen et al. (4, 5), with heterogeneity variance ($\tau 2$) estimated using the maximum likelihood method.

Pooled RRs were calculated using the Mantel-Haenszel method, with exact calculations for zero cell counts as suggested by Cooper, Hedges, and Valentine (2009) and Sweeting, Sutton, and Lambert (2004) (6-8). A Hartung-Knapp adjustment was applied for conservatism (9) (10). Heterogeneity ($\tau 2$) was estimated using the Paule-Mandel method with Q profile for confidence intervals (11, 12).

Forest plots illustrated meta-analysis outcomes, with prediction intervals indicating future study effects. Higgins and Thompson's I2 statistics assessed heterogeneity (13). Outlier detection and model fitting exploration were conducted as recommended by Harrer et al. (14). Publication bias was assessed using Funnel plots and Egger's test with a significance level of 10%.

We constructed a cohort from case reports and case series. The cohort analysis involved one-sample one-sided t-tests for mean percentage repigmentation with Bonferroni-Holm correction and ANOVA for intergroup comparisons, with $\alpha = 0.05$. All analyses were performed in R (v4.1.2) using base R functions, meta (v6.2-1), and dmetar (v0.0.9000) packages (5, 15, 16).

Figure S1. Forest plot of the number of patients who experienced adverse events leading to discontinuation of treatment.

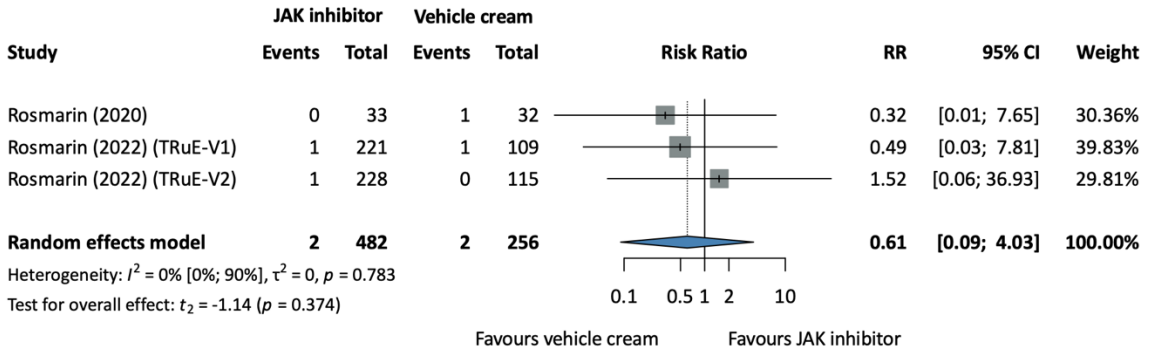
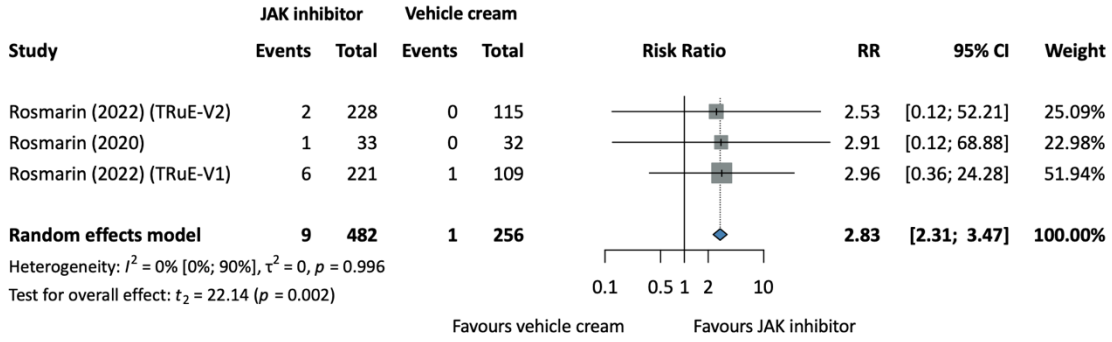


Figure S2. Forest plot of the number of patients who experienced serious adverse events.



Risk of Bias (RoB) Assessment for RCTs

Table S2: Domain-level judgements of the efficacy outcome (achieving 75% improvement in the F-VASI score) for each study.

Study	Interventions	D1: Randomisation process	D2: Deviations from intended interventions	D3: Missing outcome data	D4: Measurement of the outcome	D5: Selection of the reported results	Overall assessment
Rosmarin 2020	JAK inhibitor vs vehicle cream	+	+	+	+	+	+
Rosmarin 2022 (TRuE – 1 & TRuE – 2)	JAK inhibitor vs vehicle cream	+	+	+	+	+	+

Table S3: Domain-level judgements of the adverse events outcome (any adverse events) for each study.

Study	Interventions	D1: Randomisation process	D2: Deviations from intended interventions	D3: Missing outcome data	D4: Measurement of the outcome	D5: Selection of the reported results	Overall assessment
Rosmarin 2020	JAK inhibitor vs vehicle cream	+	+	+	+	+	+
Rosmarin 2022 (TRuE – 1 & TRuE – 2)	JAK inhibitor vs vehicle cream	+	+	+	+	+	+

Table S4. Basic characteristics of all non-randomised trials

First Author	Study site	Study type	Study period	Population	Number of analysed patients	Male (n)	Mean age (SD)	Treatment received	Combination
Xinhong Su	China	Single-arm trial	2023	Diagnosis of vitiligo who failed previous systemic steroids, calcineurin inhibitors or phototherapy for ≥ 3 months.	12	7	31.3 (13)	Upadacitinib (15 mg qd)	Nil
Fang	Taiwan	Single-arm trial	2022	Non-segmental vitiligo with no new depigmentation for ≥ 3 months and no phototherapy for 1 month before treatment.	3	2	36.6 (19)	Tofacitinib (5 mg qd)	Excimer light (308 nm 3/week)
Dong	China	Single-arm trial	2022	Non-segmental progressing vitiligo. Previously received systemic or topical steroids, traditional Chinese medicine, topical calcineurin inhibitors, NB-UVB.	4	3	26.5 (6.1)	Baricitinib (4 mg 4wk → 2 mg 8wk)	UVB (150 mJ/cm2)
Fang	Taiwan	Pilot study	2021	Four Asian patients with no new depigmentation for ≥ 3 months. Previously received treatment including phototherapy.	4	2	43 (15)	Tofatcitinib (5 mg/qd)	Nb-UVB
Mobasher	USA	Single-arm trial	2020		16	8		Tofatcitinib 2%	NB-UVB (7), PUVA (1), topical steroid (3), topical calcineurin inhibitor (4), herbals (1)
Joshipura	USA	Open-label extension study	2018	Patients with recent vitiligo treatment exposure were required to wash out of treatment within	8	4	50 (NA)	Ruxolitinib (1.5%)	NB-UVB (3)

				designated time frames (topical treatment, 2 weeks; immunomodulating oral medications, 4 weeks; laser and light treatment, 8 weeks; and investigational/biologic therapies, 12 weeks)					
Gianfaldoni	Italy, Germany, Croatia, Bulgaria, USA, Australia	Retrospective study	2018	Stable or active vitiligo Vulgaris by more than 2 years and less than 10. In the recent past (more than 5 months), none of them had been treated for the cutaneous disease.	9	NA	NA	Tofatcitinib 10 mg/qd	Phototherapy
Rothstein	USA	Open-label proof-of-concept trial	2017	Patients with recent vitiligo treatment exposure were required to wash out of treatment within designated time frames (topical treatment, 2 weeks; immunomodulating oral medications, 4 weeks; laser and light treatment, 8 weeks; and investigational/biologic therapies, 12 weeks)	11	6		Ruxolitnib (2%)	x
McKesey	USA	Pilot study	2019	All patients had previously tried ≥ 3 months of treatment with topical corticosteroids or calcineurin inhibitors in addition to NB-UVB phototherapy or sunlight exposure 3 times weekly without improvement of their disease.	11	6	44	Tofatcitinib 2%	NB-UVB

Song	China	Observational study	01.2019-11.2021	No systemic treatment or phototherapy in the past 4 weeks.	34	9	NA	Tofatcitinib (5 mg/bid)	Halomethasone, tacrolimus (1.5%), pimercolimus, NB-UVB

Figure S3. Forest plot of the mean percentage repigmentation in vitiligo lesions of the patients included in the single-arm trials employing only JAK inhibitors.

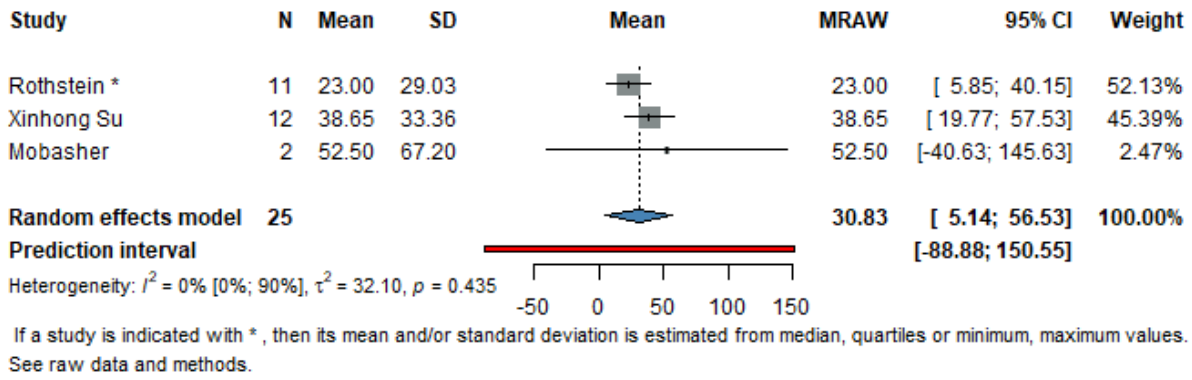


Figure S4. Forest plot of the mean percentage repigmentation in vitiligo lesions of the patients included in the single-arm trials employing JAK inhibitors and UVB.

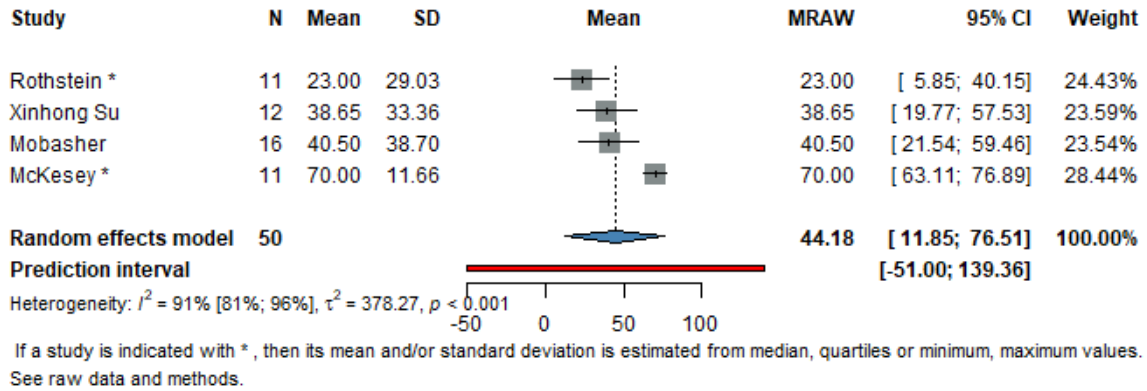
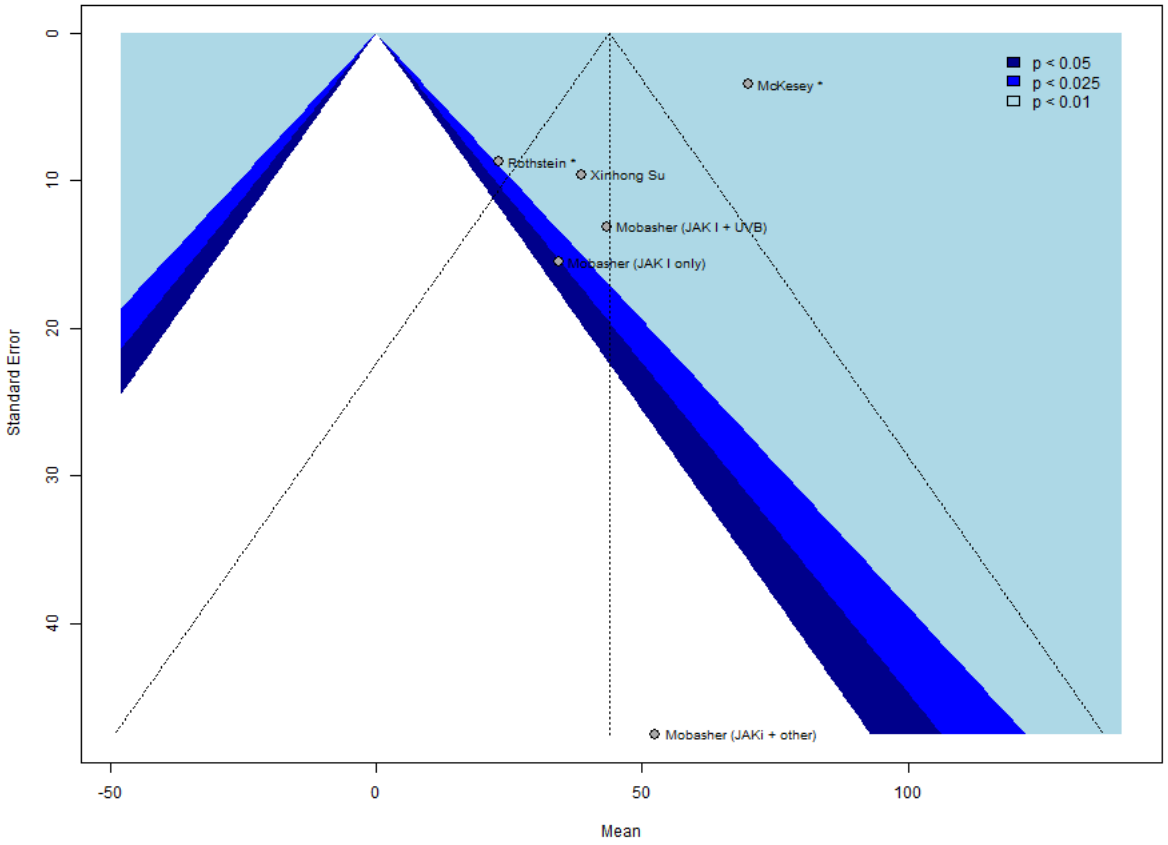


Figure S5. Funnel plot of the single-arm trials assessing the efficacy of JAK inhibitors in vitiligo.



Risk of Bias (RoB) Assessment for single-arm trials

Table S5: Domain-level judgements of the efficacy outcome (percentage change in VASI score) for each study.

Study	Interventions	D1: Bias due to confounding	D2: Selection of participants	D3: Classification of interventions	D4: Deviation from intended interventions	D5: Missing data	D6: Measurement of outcomes	D7: Selection of reported results	Overall risk of bias
Xinhong Su (2023)	Oral JAK inhibitor (upadacitinib)	Low	Low	Low	Low	Low	Low	Low	Low
Mobasher (2020)	Topical JAK inhibitor (tofacitinib)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
McKesey (2019)	Topical JAK inhibitor (tofacitinib)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Rothstein (2017)	Topical JAK inhibitor (ruxolitinib)	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Table S6. Basic characteristics of all case reports and case series

First Author	Study site	Study type	Study period	Area affected	Gender	Age	Previous treatment	Treatment received	Combination
Xu	China	Case report	2023	Entire body	F	40	Systemic GC, topical calcineurin inhibitor, 308 nm excimer laser, NB-UVB	Tofatcitinib (5 mg)	NB-UVB
Pan	China	Case report	2023	Face, neck, chest, extremities	M	16	Nil	Upadacitinib (15 mg)	Crisaborole
Maurakami	Japan	Case report	2023	Scalp	M	53	Systemic GC, squaric acid dibutylester topical	Delgocitinib (0.15%)	Excimer laser
Li	China	Case report	2023	Trunk and extremities	F	17	Topical steroids, tacrolimus, calcipotriol, systemic corticosteroids combined with NB-UVB phototherapy, oral compound glycyrrhizin tablets, and Chinese herbs	baricitinib (2mg bid)	Tacrolimus (0.1% bid) NB-UVB
				Face, trunk	F	56	Oral Chinese herbs, topical tacrolimus 0.1%, caloripuncture, oral ginkgo biloba 80mg bid, mometasone furoate cream, NB- UVB	Baricitinib (2 mg bid)	Tacrolimus (0.1%), ginkgo biloba (80 mg/bid)

Camacho	USA	Case report	2023	Eyelids	M	8	NA	Ruxolitinib (1.5% bid)	NA
Aickara	Italy	Case report	2023	Face, scalp, trunk, extremities	M	66	Tacrolimus 0.1%, pimercrolimus 0.1%, twice weekly phototherapy NB-UVB,	Tofacitinib (5 mg bid)	Tacrolimus (0.1%), pimercolimus (0.1%)
Yagi	Japan	Case report	2021	Neck, hands	M	39	Topical steroids, NB-UVB	Delgocitinib	NA
				NA	F	45	NB-UVB	Delgocitinib	NA
Scheinberg	Brazil	Case report	2021	Face, hands, arms, neck	F	30	NA	Tofacitinib (5 mg bid)	NA
Moore	USA	Case report	2021		F	56	Alpha lipoic acid, vitamin C, vitamin E, polypodium leucotomos extract, and topical pimecrolimus 1% cream for 6 weeks before initiation of narrowband ultraviolet B (NBUVB) and excimer laser therapy	Tofacitinib (5 mg bid)	Alpha lipoic acid, vitamin C, vitamin E, polypodium leucotomos extract, and topical pimecrolimus 1% cream for 6 weeks before NB-UVB and excimer laser therapy

Berbert Ferreira	Brazil	Case report	2021	Face	M	17	Oral corticosteroids, antioxidants, oral vit D, topical tacrolimus, NB-UVB	Tofacitinib (5 mg bid)	NB-UVB
Tajalli	USA	Case report	2020	Face, chest, elbows, hands	M	30	Phototherapy, topical tacrolimus and steroids	Tofacitinib (5 mg bid)	NB-UVB
Olamiju	USA	Case report	2020	Chin and neck	M	4	Alclometasone 0.05%	Tofacitinib 2%	NB-UVB
Mumford	Australia	Case report	2020	Hands and forearms	M	67	None	Tofacitinib 5 mg bid	NA
komnitski	Brazil	Case report	2020	Face, neck, elbows, hands, feet	F	40	Phototherapy, NB-UVB, systemic steroids	Tofacitinib 5 mg bid	NA
Kim	USA	Case report	2018	Face, chest arms, forearms, shins, hands	F	33	NA	Tofacitinib 5 mg bid	NB-UVB
Joshipura	USA	Case report	2018	Face	M	49	NA	Ruxolitinib 1.5%	NA

				Entire body	F	43	NA	Tofacitinib 5 mg bid	NA
Hu	China	Case report	2018	Perioral	M	8 months	NA	Tofacitinib 1.5% bid	NA
				Halo nevus on trunk	M	12	NA	Tofacitinib 1.5% bid	NA
Vu	Australia	Case report	2017	NA	M	44	Prednisolone 50 mg, NB-UVB, betamethasone dipropionate ointment	Tofacitinib 5 mg bid	Prednisolone 50 mg, NB-UVB, betamethasone dipropionate ointment
Harris	USA	Case report	2016	Face, scalp, extremities	M	35	NA	Ruxolitinib 20 mg bid	NA
Liu	USA	Case series	2017	Face, torso, arms, hands, feet, legs	F	54	NB-UVB, topical tacrolimus	Tofacitinib	x
				Face, torso, arms, hands, feet, legs	M	45	Prednisone	Tofacitinib	x

				Face, torso, arms, hands, feet, legs	F	46	NB-UVB, topical steroids, pseudocatalase cream, blister grafting	Tofacitinib	NB-UVB
				Face, neck, torso, hands, feet	F	55	NB-UVB, secukinumab	Tofacitinib	x
				Torso, elbows, hands	M	45	NB-UVB, topical tacrolimus	Tofacitinib	NB-UVB
				Face, neck, arms, hands, legs	M	28	NB-UVB, topical steroids, topical tacrolimus	Tofacitinib	x
				Face, neck, arms, hands, legs	F	47	NB-UVB, excimer laser, topical PUVA, topical steroids	Tofacitinib	x
				Forehead, torso, arms, hands, legs	M	49	NB-UVB, topical steroids, topical tacrolimus	Tofacitinib	x
				Lower forehead eyelids, perioral, axillae, elbows, hands, lower back, gluteal cleft, feet	M	32	NB-UVB, fraxel laser, cryotherapy, topical tacrolimus	Tofacitinib	x

				Entire body	F	73	NB-UVB, PUVA	Tofacitinib	x

Table S7. Patient characteristics of the cohort assembled from case reports and case series.

	n	Age (years)	Follow-up time (months)		Vitiligo duration (months)	
		Median [IQR]	**Mean**	**Median [IQR]**	**Mean**	**Median [IQR]**
total	28	37.5 [28.8-49.8]	8 (n=28)	6 [3 - 11]	117.9 (n=24)	90 [45 - 174]
male	15 (53.6%)	32 [26-42]	6.3 (n=15)	4 [3 - 8]	102.7 (n=14)	90 [39 - 162]
female	13 (46.4%)	46 [33-55]	10 (n=13)	9 [4 - 11]	139.2 (n=10)	72 [48 - 216]

Table S8. Mean percentage repigmentation of vitiligo lesions in the patients included in the cohort.

Group	Intervention	n	Mean percentage repigementation	CI min	CI max	p-value
A	JAK inhibitor alone	13	48.7%	0.28	∞	0.002
B	JAK inhibitor + UVB	11	63.7%	0.49	∞	<0.001
C	JAK inhibitor + other	4	56.3%	0.18	∞	0.061

Table S9. GRADE assessment for efficacy and adverse events

Patient or population: patients with vitiligo

Setting: Systematic review and meta-analysis

Intervention: JAK inhibitor

Comparison: placebo, vehicle cream or conventional treatment

Outcomes	№ of participants (studies)	Relative effect (95% CI)	Absolute (95% CI)	Certainty of the evidence (GRADE)
Efficacy (RCTs)	476 (3 RCTs)	**RR 3.47** (0.98 to 12.22)	**198 more per 1,000** (from 2 fewer to 898 more)	⨁⨁⨁◯ Moderate
Efficacy (Single-arm trials)	50 (4 single-arm trials)	not estimable	**44 more per 1,000** (from 24 fewer to 63 more)	⨁◯◯◯ Very low
Adverse events	476 (3 RCTs)	NA	**107 more per 1,000** (from 47 fewer to 324 more)	⨁⨁⨁⨁ High

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; RR: risk ratio; RCT: randomised controlled trial

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