

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Tacrolimus for the Treatment of Adults with Psoriasis or Vitiligo: A Review of the Clinical and Cost-Effectiveness

Service Line: Rapid Response Service
Version: 1.0
Publication Date: October 11, 2017
Report Length: 21 Pages

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Cite As: *Tacrolimus for the Treatment of Adults with Psoriasis or Vitiligo: A Review of the Clinical and Cost-Effectiveness*. Ottawa: CADTH; 2017, Oct. (CADTH rapid response report: summary with critical appraisal).

Acknowledgments:

ISSN: 1922-8147 (online)

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Context and Policy Issues

Psoriasis is a chronic inflammatory skin condition with a complex multifactorial etiology and multiple subtypes. The prevalence of psoriasis ranges between 1% to 2% for European populations and 0.1% to 0.3% for Asian populations.¹ The most commonly diagnosed subtype of psoriasis, accounting for approximately 90% of cases, is chronic plaque psoriasis typically characterized by thick, raised, well demarcated, erythematous plaques. Comorbidities of psoriasis include psoriatic arthritis, cardiovascular disease, and psychosocial sequelae leading to a negative impact on patient quality of life.¹ Current treatment options are not curative; however, a range of treatment options, including vitamin D preparations, corticosteroids, and phototherapy, have demonstrated effective management of mild disease.²

Vitiligo is a skin condition characterized by patchy skin depigmentation that may additionally affect hair follicles.³ Worldwide prevalence of vitiligo has been estimated to be between 0.5% and 2%.⁴ Vitiligo can manifest as generalized vitiligo, the common symmetrical subtype, and segmental, affecting one side of the body. Vitiligo involves a complex pathophysiology likely involving autoimmune reactions with melanocytes.^{4,5} Like psoriasis, vitiligo presents psychosocial sequelae impacting quality of life and resistance to current non-curative treatment options is common.⁶ Treatment options include topical corticosteroids and immunomodulators, phototherapy, excimer laser, surgery, and nonmedicinal cosmetic camouflage.⁴

Tacrolimus is a calcineurin inhibitor which suppresses T-cell activation and is indicated for the treatment of atopic dermatitis and a variety of other skin disorders.² Topical tacrolimus is absorbed by the skin and is well tolerated.⁷ Currently approved for use in atopic dermatitis, tacrolimus efficacy is increasingly studied for off-label indications including psoriasis and vitiligo.^{8,9} More effective treatment options for these conditions with fewer adverse effects and increased compliance would be welcomed.¹⁰

The purpose of this report is to retrieve and review the existing clinical effectiveness evidence for the treatment of adult psoriasis and adult vitiligo patients with tacrolimus as compared to placebo or other active treatment. Additionally, this report aims to retrieve and review cost-effectiveness evidence for the treatment of adult psoriasis and adult vitiligo patients with tacrolimus.

Research Questions

1. What is the clinical effectiveness of tacrolimus for the treatment of adults with psoriasis?
2. What is the clinical effectiveness of tacrolimus for the treatment of adults with vitiligo?
3. What is the cost-effectiveness of tacrolimus for the treatment of adults with psoriasis?
4. What is the cost-effectiveness of tacrolimus for the treatment of adults with vitiligo?

Key Findings

The evidence identified in this report was limited by methodological quality and was heterogeneous regarding patient population and comparators. However, this evidence consistently suggested that tacrolimus demonstrated clinical effectiveness for the treatment of different manifestations of adult psoriasis and adult vitiligo. Evidence from randomized controlled trials suggested that topical tacrolimus was superior to topical pine tar for head and face plaque psoriasis, and demonstrated similar efficacy to topical calcipotriol for chronic plaque psoriasis. For adult vitiligo, randomized controlled trials of fewer than 40 patients did not identify a significant difference between topical tacrolimus and topical pimecrolimus, or topical mometasone furoate in outcomes of repigmentation. One randomized controlled trial of 72 vitiligo lesions also supported the use of topical tacrolimus for prevention of depigmentation of successfully treated lesions. While adverse events of topical tacrolimus in psoriasis patients were not well documented in the identified evidence, the adverse event observations for adult vitiligo patients were consistent and tacrolimus was regarded as safe by study authors. No evidence regarding the cost-effectiveness of tacrolimus for adult psoriasis or adult vitiligo was identified. Additional high quality clinical trials are required to provide definitive conclusions regarding the clinical efficacy and safety of tacrolimus for adult psoriasis and adult vitiligo patients.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Embase, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and September 11, 2017.

Literature Search Methods

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients requiring treatment for psoriasis or vitiligo
Intervention	Tacrolimus (e.g., Protopic)
Comparator	Active comparators and/or placebo
Outcomes	Clinical effectiveness, clinical benefit and harm, and cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and economic evaluations.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool,¹¹ while randomized and non-randomized studies were critically appraised using the Downs and Black Checklist.¹² Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 231 citations were identified in the literature search. Following screening of titles and abstracts, 203 citations were excluded and 28 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 24 publications were excluded for various reasons, while seven publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study Design

Of the included publications, four were systematic reviews (SRs),^{1,4,13,14} and three were clinical studies.^{3,15,16} Three of the four SRs contained meta-analysis (MA) and only selected randomized controlled trials (RCTs) for inclusion.^{1,4,14} The most recently published SR was published in 2016 and included all study designs.¹³ Of the three clinical studies included in this report two were RCTs,^{3,15} and one was a retrospective comparative study.¹⁶ One RCT was single-blinded, with randomization done at the lesion level on 18 patients who completed the study.¹⁵ Cavalié et al. published the results of a double-blind RCT that randomized 35 patients to receive topical therapy.³ The retrospective comparative study was the largest clinical study and examined 276 patient records.¹⁶ No economic evaluations of tacrolimus were identified.

Country of Origin

Authors of one SR were based in Italy.¹³ The remaining three SRs were published by the Cochrane Database of Systematic Reviews, two with author contact information from the UK,^{1,4} and one with author contact information from Germany.¹⁴ The included clinical studies were conducted in Thailand,¹⁵ Korea,¹⁶ and France.³

Patient Population

Two SRs examined evidence for vitiligo patients of any age.^{4,13} Psoriasis patients of any age were the population of interest in the remaining two SRs.^{1,14} One focused on scalp psoriasis,¹⁴ and one focused on chronic plaque psoriasis.¹ The three clinical studies

examined vitiligo patients.^{3,15,16} Two studies included only adult patients.^{3,15} One study included a mixed age population but provided data relevant to adult vitiligo patients.¹⁶ All studies provided further definitions for patient inclusion criteria including symmetrical nonacral vitiligo,¹⁵ nonsegmental vitiligo,¹⁶ and patients with 75% treatment repigmentation of at least one lesion.³ The RCT that included patients with successfully treated vitiligo lesions did not specify which treatment was previously successfully used on enrolled patients.³ This RCT also excluded patients with segmental vitiligo, spontaneous repigmentation, and tacrolimus contraindications which were not provided.³

Interventions and Comparators

The interventions of interest in the included SRs were very broad with the exception of Sisti et al.,¹³ where topical tacrolimus interventions, excluding those in a combination therapy, were examined. One SR did not specify any specific intervention of interest when identifying evidence for vitiligo treatments,⁴ whereas the remaining two SRs specified topical treatments for psoriasis.^{1,14} Three of the SRs examined evidence against any comparator.^{4,13,14} One SR searched the literature for evidence comparing any topical treatment intervention for psoriasis to a placebo or to vitamin D preparations.¹

The identified clinical studies investigated the clinical effectiveness of topical 0.1% tacrolimus applications,^{3,15,16} including twice per day,^{15,16} and twice weekly.³ Follow-up averaged 9.6 months in the retrospective study,¹⁶ and treatment duration in the RCTs was six months.^{3,15} Silpa-Archa et al compared 0.1% topical tacrolimus to 0.1% topical mometasone furonate.¹⁵ The RCT that examined twice weekly applications of tacrolimus compared its clinical efficacy to a placebo.³ The retrospective comparative study examined patients that had been treated with topical tacrolimus as compared to patients treated with a 308nm excimer laser twice weekly, and to patients treated with both excimer laser and topical tacrolimus.¹⁶

Outcomes

Outcomes examined in the SRs included repigmentation,^{4,13} response rate,^{13,14} improvement time,¹³ Investigator's Global Assessment of Disease Severity (IGA),¹⁴ Total Severity Score (TSS),¹⁴ various quality of life measures (QoL),^{1,4,14} Patient Global Assessment of Disease Severity (PGA),¹⁴ Investigator's Assessment of Overall Global Improvement (IAGI),¹ Patient Assessment of Overall Global Improvement (PAGI),¹ duration of response,^{4,14} cessation of spread and new lesions,⁴ Psoriasis Disability Index,¹ patient withdrawals from the studies,¹ and adverse event data was examined in three of the four SRs.^{1,4,14} Not all outcome data were identified in relevant studies included in the SRs. Repigmentation was not defined in one trial included in Sisti et al.;¹³ however, it was measured by serial mapping of body lesions and determining a percentage of repigmented area in a relevant trial identified by Whitton et al.⁴ The outcome of clearance for psoriasis patients was determined by the IGA with higher scores reflecting more severe disease, and otherwise was left undefined.¹⁴ IAGI and PAGI were defined by Mason et al. as improvement from baseline and were variably defined in the included studies ranging from a four point to a seven point scale. These scales were used frequently in the identified literature with higher scores indicating greater improvement.¹

The included comparative studies reported outcomes of repigmentation,^{15,16} depigmentation,³ PGA,³ QoL,³ and two of the three clinical studies included at least some information on adverse events.^{3,15} While no objective measurement methodology was mentioned in the two clinical studies reporting repigmentation outcomes, it was assessed in

duplicate using photographs in both studies.^{15,16} PGA was also assessed in duplicate using photographs, and the evolution of vitiligo was categorized as depigmentation, no change, or repigmentation.³ QoL was assessed using the Dermatology Life Quality Index score.³

A summary of these study characteristics is presented in Appendix 2.

Summary of Critical Appraisal

All the included SRs have a few limitations.^{1,4,13,14} The one SR that did not include an MA, Sisti et al., was limited by the inclusion of evidence from lower quality studies including case reports. This SR also did not present any quality assessment of the included literature or present a flowchart to outline the literature selection process.¹³ However this SR did provide details of a systematic literature search, inclusion and exclusion criteria, and search terms. The data extraction was described and conducted in triplicate, study characteristics were tabulated, the research question was defined, the patient population of interest was described, adverse event data was reported, and the SR contained a statement of no conflicts of interest (COIs).¹³ The remaining three SRs were part of the Cochrane Database of Systematic Reviews and therefore followed a similar format fulfilling most of the AMSTAR quality criteria.^{1,4,14} All three did have at least one author with a stated COI. While a publication bias assessment was not done in these three SRs,^{1,4,14} two of them report that it was due to an insufficient number of publications.^{4,14} These SRs had many strengths including a well described systematic literature search methodology, a flowchart that described the literature selection process, a valid critical appraisal system was applied, a discussion of the limitations of the SR was provided, the research question and patient population were sufficiently described, and adverse event data from the selected RCTs were reported.^{1,4,14} All three also provided data extraction methodology,^{1,4,14} two of which conducted the data extraction in duplicate.^{1,14} Tabulated study characteristics were provided for studies included in the SR and also studies that were excluded.^{1,4,14} These three SRs conducted MAs that assessed statistical heterogeneity, and described the statistical methods used.^{1,4,14} A sensitivity analysis was conducted by two of these three Cochrane Collaboration SRs. One analysis examined the impact of using within-patient studies on pooled findings,¹ while another examined the potential impact of methodological aspects of included studies such as intention-to-treat (ITT) analysis and allocation concealment on pooled data.¹⁴

Sisti et al. identified four relevant studies of adult vitiligo patients the description of which was limited to one prospective placebo-contralateral-controlled study, one undescribed open-label study, one prospective open-label study, and one open randomized study. A quality assessment of these studies was not provided.¹³ Schlager et al. identified one relevant RCT on adult plaque psoriasis of the head and face. The authors assessed this relevant RCT as at an unclear risk of selection bias (unclear random sequence generation and no mention of allocation concealment), unclear performance bias (no mention of blinding), unclear detection bias (no mention of outcome assessment blinding), however the authors found the RCT at low risk of attrition bias, reporting bias, and other biases.¹⁴ Whitton et al. also identified one relevant RCT assessed as at high risk of performance and detection bias as it was an open-label study. High risk of bias was also identified in this RCT due to a lack of ITT analysis, and an unclear risk of selection bias due to a lack of information on allocation concealment. The RCT did fulfill quality criteria for random sequence generation, and outcome assessment blinding.⁴ Mason et al. also identified a single RCT fulfilling the inclusion criteria of this report, a single-blind RCT on adult chronic plaque psoriasis patients.¹ The RCT was assessed having an unclear risk of selection bias

(insufficient details of allocation concealment), and an unclear risk of performance bias and detection bias (due to single-blinded design). The RCT did fulfill quality criteria for randomization methodology, no loss to follow-up, and a lack of baseline differences between patient groups.¹

The RCTs identified and included in this report shared some significant limitations including insufficient description of the randomization process, a lack of information on allocation concealment, and no information on patient compliance.^{3,15} The RCT by Silpa-Archa et al. was also limited by undefined patient inclusion and exclusion criteria, no ITT analysis, and no *a priori* statistical power calculation.¹⁵ The double-blind RCT, Cavalie et al., 2015, had the lowest number of evidence quality limitations but acknowledged COIs, and had limited reporting of adverse events.³ The RCTs shared strengths including blinded outcome assessment, tabulated patient characteristics, sufficiently described interventions and outcomes, and reported statistical methodology.^{3,15} Additional strengths of some of the identified RCT evidence included a discussion of study limitations,^{3,15} a patient recruitment flowchart,³ patient inclusion criteria,³ an *a priori* statistical power calculation,³ ITT analysis,³ and a statement of no COIs.¹⁵ While Cavalie et al. provided ITT analysis it is not clear if PP or ITT analysis was used for some outcomes, and conclusions of statistical significance were based upon PP analysis.³ One of the four comparative clinical studies, Park et al., was a retrospective comparative study and therefore had limitations inherent to retrospective design including selection and reporting bias. Patient selection and allocation were undefined, and it was an open-label study. Although patient characteristics for all patients were tabulated, this study did not provide characteristics of patient study groups. Baseline differences between groups were not reported. This study also did not provide any information on adverse event data. The strengths of this study included known compliance, statistical methodology, a multivariate analysis, a discussion on the limitations of the study, and a statement of no COIs. This study was also the largest identified study and reported data compiled from 276 patient records.¹⁶

Summary of Findings

What is the clinical effectiveness of tacrolimus for the treatment of adults with psoriasis?

Two SRs identified one RCT each that examined tacrolimus for the treatment of adult psoriasis.^{1,14} One RCT compared 0.1% topical tacrolimus to 5% topical pine tar in 40 patients and found a statistically significant improvement in psoriasis clearance and number needed to treat to benefit with tacrolimus.¹⁴ The other identified RCT compared 0.1% topical tacrolimus to 0.005% topical calcipotriol in 124 patients and found no statistically significant differences in outcomes of IAGI, PAgI, or adverse events. While patient withdrawals due to adverse events and patient withdrawals due to treatment failure were not statistically different between treatment groups, total patient withdrawals were significantly greater in tacrolimus treated patients.¹

What is the clinical effectiveness of tacrolimus for the treatment of adults with vitiligo?

The SR by Sisti et al. identified four clinical studies that investigated tacrolimus treatment of vitiligo in adult patients. Two of the studies were comparative studies; however, comparative clinical efficacy outcome reporting was unclear. One prospective placebo controlled study was reported as observing an overall repigmentation of 60.5% in responding patients, and that 77% demonstrated repigmentation. Another study was an open randomized study where all tacrolimus-treated vitiligo patients obtained variable degrees of lesion repigmentation. No additional comparative information was provided.

Adverse events were also reported without comparative data. Transient facial flushing in 16 of 30 patients, enhanced heat intolerance in 9 of 30 patients, burning in 4 of 30 patients, and mild perioral folliculitis in 2 of 30 patients was observed in the treatment group of this prospective placebo controlled study. Adverse events reported in the open randomized study identified by Sisti et al. were heat sensation (9/12), soreness (1/12), pruritus (1/12), bulbar conjunctive erythema (1/12), and redflushing (5/12). Clinical effectiveness in one relevant non-comparative study identified by Sisti et al. included more than 75% repigmentation in 61% of vitiligo patients treated with 0.1% topical tacrolimus, with over 95% of patients experiencing at least 25% repigmentation. Another non-comparative study, an open-label prospective study of 20 patients, qualitatively observed that all patients that completed the study period had some improvement in lesion size and follicular repigmentation. No adverse events were reported from the two non-comparative studies.¹³ Whitton et al. identified one RCT that examined the clinical efficacy of 0.1% topical tacrolimus as compared to 1% topical pimecrolimus in 25 randomized adult vitiligo patients. No statistically significant difference was observed in the frequency of greater than 75% of facial lesion repigmentation between these two calcineurin inhibitors. Adverse events were comparable with a burning sensation adverse event more common in the tacrolimus treated patients (9/12) as compared to the pimecrolimus treated patients (4/13). The authors of the SR conclude that the evidence supports topical tacrolimus as a reasonable alternative to topical corticosteroids especially for lesions in locations where topical corticosteroids pose a higher risk of adverse effect. This conclusion was not based upon studies that only included adult patients.⁴

A single-blinded RCT on 20 adult patients with symmetrical nonacral vitiligo compared 0.1% topical tacrolimus to 0.1% topical mometasone furonate on randomized lesions. There was no statistically significant difference in the degree of repigmentation of randomized lesions between the treatment groups at the six month study end; however, at two months 44% of mometasone lesions had repigmentation as compared to 17% of tacrolimus lesions (statistical significance not reported). While repigmentation was assessed every two months until the end of the six month treatment period no additional outcome data were reported for these interval assessments. None of the tacrolimus treated lesions had telangiectasia as compared to 33% of the mometasone treated lesions; this represented a statistically significantly increased frequency of telangiectasia in the mometasone group. The authors conclude that they did not observe a difference in repigmentation, and tacrolimus demonstrated fewer adverse effects in this small pilot study. Additionally the authors make a cost-related comment that mometasone may be an appropriate choice for patients unable to afford tacrolimus.¹⁵

Cavalié et al. examined the efficacy of twice weekly applied topical tacrolimus applications, as compared to placebo, to prevent depigmentation of successfully treated lesions in 35 randomized patients. The ITT analysis of 72 lesions failed to demonstrate a statistically significant difference in the rate of depigmentation; however, the per-protocol analysis of 56 lesions demonstrated that 9.7% depigmentation of tacrolimus treated lesions compared to 40.0% of placebo treated lesions was a statistically significant difference. Statistically significant differences in PGA scores also favoured tacrolimus over placebo; however, it was not reported whether this was by ITT or PP analysis. Both patient groups experienced slight QoL improvements but the difference was not significant. There were four patient withdrawals in the tacrolimus patient group as compared to one in the placebo treated group. None were reported as treatment related. Three patients in the tacrolimus group and one in the placebo group reported adverse events. Mild and transient erythema, and

stinging and burning sensations that did not require management were not clearly reported per patient or per treatment group.³

One retrospective comparative study enrolled vitiligo patients of any age; however, upon multivariate analysis patient age was revealed to be not statistically associated with outcome. The analysis does not provide evidence that it was sufficiently powered to exclude an association; however, the results are reported here as the results from this population are not statistically associated with age. Examination of records from 275 vitiligo patients found that repigmentation of over 50% was achieved in 17 of 109 patients using tacrolimus; however, significantly more patients experienced over 50% repigmentation using a combination of excimer laser and tacrolimus. Excimer laser alone was associated with over 50% repigmentation in 30 of 100 vitiligo patients. A statistical comparison to the tacrolimus alone group was not reported; however, in a multivariate analysis of treatment of less than six months and more than six months there was no statistically significant difference between tacrolimus and excimer laser treatment. Additionally the combination of tacrolimus and excimer laser did not provide statistically superior repigmentation outcomes as compared to tacrolimus alone for treatment periods of six months or more. Adverse events were not reported.¹⁶

What is the cost-effectiveness of tacrolimus for the treatment of adults with psoriasis?

No evidence on the cost-effectiveness of tacrolimus for the treatment of adults with psoriasis was identified.

What is the cost-effectiveness of tacrolimus for the treatment of adults with vitiligo?

No evidence on the cost-effectiveness of tacrolimus for the treatment of adults with vitiligo was identified.

Limitations

The evidence identified in this report was limited by trial methodological quality and small patient sample sizes. Less frequent adverse events may have not been identified in the included small trials. Heterogeneity between studies with regard to patient populations and outcome measures also limited the confirmation of efficacy and adverse event incidence and therefore limits the confidence of the conclusions in this report.

Conclusions and Implications for Decision or Policy Making

Evidence of limited quantity and quality identified in this report suggested that topical tacrolimus provided some effectiveness for psoriasis patients. While no significant difference in disease improvement was evident between tacrolimus and calcipotriol for chronic plaque psoriasis,¹ tacrolimus was superior, as compared to pine tar, for the treatment of plaque psoriasis of the head and face.¹⁴ Adverse events associated with topical tacrolimus were not well documented in the identified trials of adult psoriasis patients.^{1,14}

In the treatment of adult vitiligo, evidence identified in this report does not support differential efficacy of topical tacrolimus as compared to topical pimecrolimus,⁴ or topical mometasone furoate,¹⁵ in repigmentation outcomes. Effectiveness evidence from a larger mixed-age retrospective comparative study found no statistically significant difference between topical tacrolimus and excimer laser, or between tacrolimus and a combination of tacrolimus and excimer laser following six months of treatment.¹⁶ Evidence was also

identified supporting the efficacy of topical tacrolimus maintenance therapy for vitiligo.³ Despite the heterogeneity of trials, quality limitations, and relatively small size, the clinical evidence consistently suggested effectiveness of tacrolimus for adult vitiligo patients. Adverse event observations in tacrolimus-treated patients of burning sensations, facial flushing, soreness, pruritus, and erythema were also consistent across identified studies. Topical tacrolimus also demonstrated fewer adverse effects than topical mometasone furoate in adult vitiligo patients.¹⁵ Study authors suggested that tacrolimus demonstrated good tolerability.

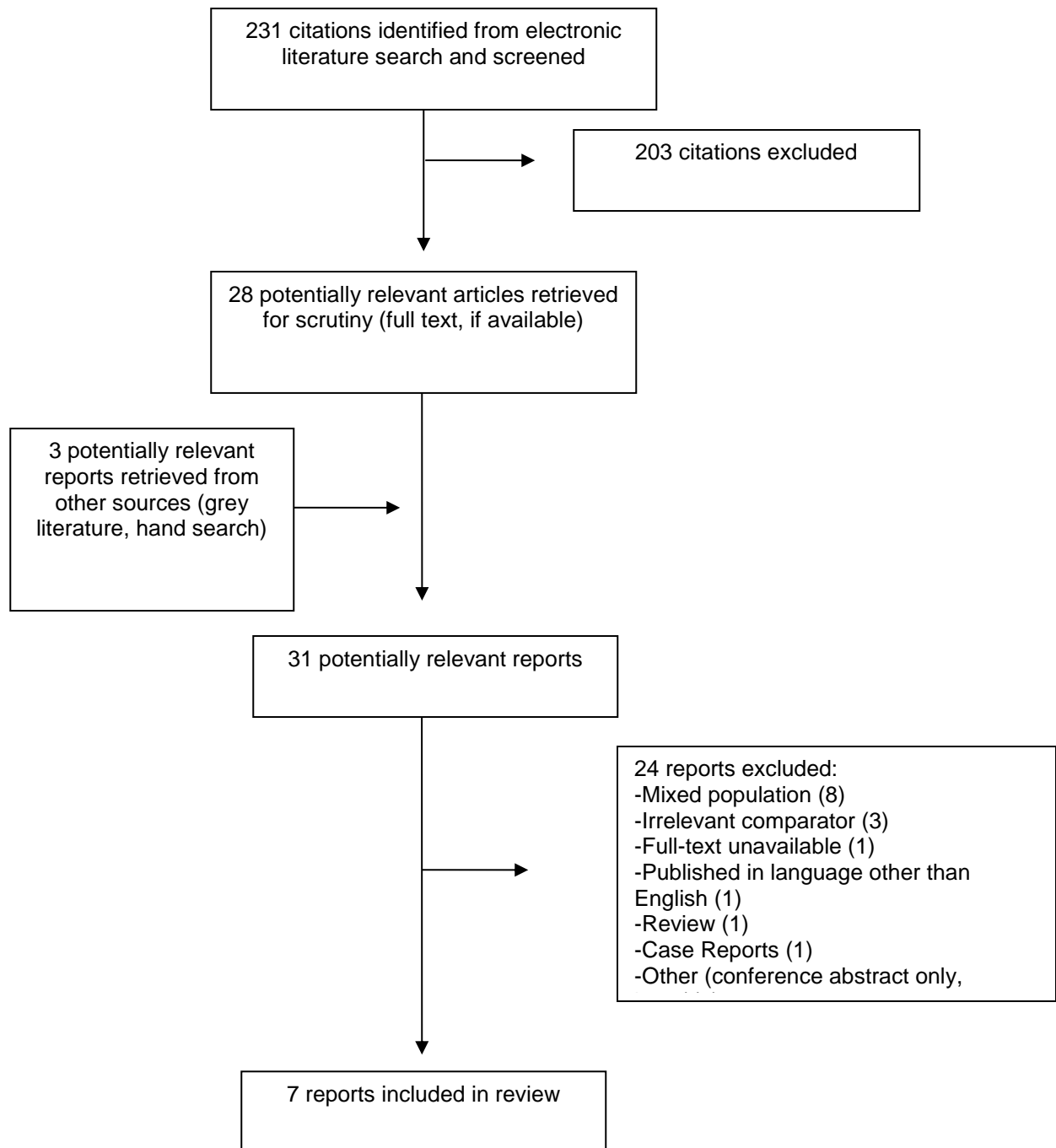
A majority of clinical studies identified in the included SRs examined the clinical effectiveness of tacrolimus for psoriasis or vitiligo in patient populations of mixed ages. One comparative retrospective study presented evidence that patient age was not associated with treatment outcome although it was likely underpowered for such an analysis.¹⁶ Clinical efficacy evidence from trials enrolling mixed age populations not included in this report may contain evidence relevant to adult psoriasis and vitiligo patients. While the evidence identified on adult psoriasis and adult vitiligo patients appears promising, additional large, high quality clinical trials are needed to provide firm conclusions.

No evidence of the cost-effectiveness of tacrolimus for adult psoriasis or adult vitiligo was identified.

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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Author, Publication Date	Study Design	Population	Intervention	Comparator(s)	Outcomes
Sisti et al., 2016 ¹³	Systematic Review, all study designs included, including case reports	Vitiligo Patients: any age	Tacrolimus topical Exclusion of combination therapies	Any	<ul style="list-style-type: none"> • Repigmentation • Improvement time • Response rate
Schlager et al., 2016 ¹⁴	Systematic Review with MA of RCTs	Psoriasis Patients: All ages with scalp psoriasis	Any topical treatments	Any	<ul style="list-style-type: none"> • IGA • Response rate • TSS • QoL measures • Adverse events • PGA • Duration of response
Whitton et al., 2015 ⁴	Systematic Review with MA of RCTs	Vitiligo Patients: any age	Any	Any	<ul style="list-style-type: none"> • QoL measures • Repigmentation • Adverse events • Cessation of spread and new lesions • Duration of response
Mason et al., 2013 ¹	Systematic Review with MA of RCTs	Psoriasis Patients: any age with chronic plaque psoriasis	Topical treatments	Placebo or vitamin D preparations	<ul style="list-style-type: none"> • QoL measures • IAGI • PAGI • Withdrawals • PDI • Adverse events

IAGI = Investigator's Assessment of Overall Global Improvement; IGA = Investigator's Global Assessment of Disease Severity; MA = meta-analysis; PDI = Psoriasis Disability Index; PGA = Patient Global Assessment of Disease Severity; PAGI = Patient Assessment of Overall Global Improvement; QoL = quality of life; RCT = randomized controlled trial; TSS = Total Severity Score.

Table 3: Characteristics of Included Clinical Studies

Author, Publication Date	Study Design	Population	Intervention	Comparator(s)	Outcomes
Silpa-Archa et al., 2016 ¹⁵	RCT, single-blinded pilot study (n = 20) Randomization was done at the level of vitiliginous sites	Vitiligo Patients INCLUSION: aged > 18 years with symmetrical nonacral vitiligo	Tacrolimus ointment (0.1%) twice daily	Mometasone furonate (0.1%)	<ul style="list-style-type: none"> • Repigmentation • Adverse events
Park et al., 2016 ¹⁶	Comparative Retrospective study (n = 276)	Vitiligo Patients: any age with nonsegmental vitiligo	Tacrolimus ointment (0.1%) (Protopic, Astellas Pharma Inc. Tokyo) twice daily	1. 308nm excimer laser (PHAROS EX-308, Ra Medical Systems, Carlsbad, CA) twice weekly 2 Both Tacrolimus ointment and 308nm excimer laser	<ul style="list-style-type: none"> • Repigmentation • Multivariable analysis including age factors
Cavalié et al., 2015 ³	RCT, double-blind (n = 35) Vitilgo patches evaluated independently	Vitiligo Patients: Aged (33 to 52 years) that had successful treatment (>75% repigmentation) EXCLUSION: segmental vitiligo, spontaneous repigmentation, tacrolimus contraindications	Tacrolimus ointment (0.1%) twice weekly maintenance therapy	Placebo	<ul style="list-style-type: none"> • Depigmentation • PGA • QoL (Dermatology Life Quality Index Score) • Adverse events

PGA = Patient Global Assessment of Disease Severity; QoL = quality of life; RCT = randomized controlled trial; TSS = Total Severity Score.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-analyses using AMSTAR¹¹

Strengths	Limitations
Sisti et al., 2016¹³	
<ul style="list-style-type: none"> • Systematic literature search methodology described with inclusion/exclusion criteria and search terms • Data extraction methodology described and conducted in triplicate • Discussion on study limitations • Defined research question and patient population • Tabulated study characteristics • Reported adverse event data • Statement of no COIs 	<ul style="list-style-type: none"> • No flowchart to describe literature selection • No critical appraisal of literature • Included case report studies
Schlager et al., 2016¹⁴	
<ul style="list-style-type: none"> • Systematic literature search methodology described with inclusion criteria and search terms, done in duplicate • Data extraction methodology described and conducted in duplicate • PRISMA flowchart of study selection provided • Provided a meta-analysis <ul style="list-style-type: none"> • Assessed statistical heterogeneity • Statistical methods described • Sensitivity analysis conducted • Valid critical appraisal system described and applied • Discussion on study limitations • Defined research question and patient population • Tabulated study characteristics (included and excluded studies) • Reported adverse event data 	<ul style="list-style-type: none"> • Not enough evidence to conduct a publication bias assessment • Some authors report a potential COI
Whitton et al., 2015⁴	
<ul style="list-style-type: none"> • Systematic literature search methodology described with inclusion criteria and search terms, done in duplicate • Data extraction methodology described • PRISMA flowchart of study selection provided • Provided a meta-analysis <ul style="list-style-type: none"> • Assessed statistical heterogeneity • Statistical methods described • Valid critical appraisal system described and applied • Discussion on study limitations • Defined research question and patient population • Tabulated study characteristics (included and excluded studies) • Reported adverse event data 	<ul style="list-style-type: none"> • Not enough evidence to conduct a publication bias assessment • Some authors report a potential COI
Mason et al., 2013¹	
<ul style="list-style-type: none"> • Systematic literature search methodology described with inclusion criteria and search terms, done in duplicate • Data extraction methodology described and conducted in duplicate 	<ul style="list-style-type: none"> • No assessment of publication bias • Some authors report a potential COI

Strengths	Limitations
<ul style="list-style-type: none"> • PRISMA flowchart of study selection provided • Provided a meta-analysis <ul style="list-style-type: none"> • Assessed statistical heterogeneity • Statistical methods described • Sensitivity analysis conducted • Valid critical appraisal system described and applied • Discussion on study limitations • Defined research question and patient population • Tabulated study characteristics (included and excluded studies) • Reported adverse event data 	

COI = conflict of interest; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT = randomized controlled trial.

Table 5: Strengths and Limitations of Randomized Controlled Trials and Non-Randomized Studies using the Downs and Black checklist¹²

Strengths	Limitations
Silpa-Archa et al., 2016¹⁵	
<ul style="list-style-type: none"> • RCT • Outcome assessment blinded, conducted in duplicate • Patient characteristics tabulated (but this was not the level of randomization) • Defined intervention and outcomes • Statistical methods described • Adverse event data provided • Mention of study limitations • Statement of no COIs 	<ul style="list-style-type: none"> • Randomization methodology not described • Undefined patient inclusion/exclusion criteria • No statistical power calculation to determine sample size • No information on compliance • No information on allocation and no allocation concealment • No ITT analysis
Park et al., 2016¹⁶	
<ul style="list-style-type: none"> • Treatments administered by investigators - no compliance concerns • Statistical methodology provided • Multivariate analysis conducted • Discussion of study limitations • Statement of no COIs 	<ul style="list-style-type: none"> • Retrospective comparative study • No randomization • Open-label study • Undefined patient inclusion/exclusion criteria • No statistical power calculation to determine sample size • No adverse event data • Patient characteristics tabulated - separate group characteristics not provided
Cavalié et al., 2015³	
<ul style="list-style-type: none"> • RCT • Patient recruitment data flowchart provided • Patient characteristics tabulated • Defined intervention and outcomes • Defined patient inclusion/exclusion criteria • Outcome assessment blinded in duplicate • Patients blinded • Statistical power calculation to determine sample size based on prior study • Statistical methodology provided • ITT analysis • Discussion of study limitations 	<ul style="list-style-type: none"> • Randomization methodology not described • No information on allocation concealment • No information on compliance • Acknowledged COI • Limited reporting of adverse events

COI = conflict of interest; ITT = intention to treat; RCT = randomized controlled trial.

Appendix 4: Main Study Findings and Author’s Conclusions

Table 6: Summary of Findings of Included Systematic Reviews and Meta-analyses

Main Study Findings	Author’s Conclusion																										
Sisti et al., 2016¹³																											
<p>Individual studies that included only adult patients (> 18 years):</p> <p><u>1. Prospective placebo-controlled right-left comparative study (n = 30) Tacrolimus (0.1%) ointment twice/day</u> Overall repigmentation 60.5% in the responding patients (77%). <u>Adverse Events</u></p> <table border="0"> <tr><td>Transient facial flushing</td><td>(16/30)</td></tr> <tr><td>Enhanced heat intolerance</td><td>(9/30)</td></tr> <tr><td>Burning</td><td>(4/30)</td></tr> <tr><td>Mild perioral folliculitis</td><td>(2/30)</td></tr> </table> <p><u>2. Open-label study (n = 22) Tacrolimus (0.1%) ointment twice/day</u> <u>Repigmentation</u></p> <table border="0"> <tr><td>Excellent (> 75%):</td><td>61%</td></tr> <tr><td>Marked (50 - 75%):</td><td>16.1%</td></tr> <tr><td>Moderate (25 - 50%):</td><td>18.4%</td></tr> <tr><td>Minimal (< 25%):</td><td>4.5%</td></tr> </table> <p><u>3. Open-label prospective study (n = 20) Tacrolimus (0.1%) ointment twice/day</u> Qualitative observations include all patients completing the study demonstrated improvements in lesion size, with follicular repigmentation in all cases.</p> <p><u>4. Open randomized study (n = 12) Tacrolimus (0.1%) ointment twice/day</u> All treated patients with vitiligo lesions localized to face, neck, and upper limbs obtained variable degrees of repigmentation. <u>Adverse Events</u></p> <table border="0"> <tr><td>Heat sensation</td><td>(9/12)</td></tr> <tr><td>Soreness</td><td>(1/12)</td></tr> <tr><td>Pruritus</td><td>(1/12)</td></tr> <tr><td>Bulbar conjunctiva erythema</td><td>(1/12)</td></tr> <tr><td>Redflushing</td><td>(5/12)</td></tr> </table>	Transient facial flushing	(16/30)	Enhanced heat intolerance	(9/30)	Burning	(4/30)	Mild perioral folliculitis	(2/30)	Excellent (> 75%):	61%	Marked (50 - 75%):	16.1%	Moderate (25 - 50%):	18.4%	Minimal (< 25%):	4.5%	Heat sensation	(9/12)	Soreness	(1/12)	Pruritus	(1/12)	Bulbar conjunctiva erythema	(1/12)	Redflushing	(5/12)	<p><i>“Although tacrolimus monotherapy seems to have good efficacy and tolerability, only small trials and case series are available in the literature. The largest study ever published in terms of the number of patients enrolled, only included 90 patients. Hence, further, standardized investigations on a greater number of patients are needed.”</i> (pp. 194)</p>
Transient facial flushing	(16/30)																										
Enhanced heat intolerance	(9/30)																										
Burning	(4/30)																										
Mild perioral folliculitis	(2/30)																										
Excellent (> 75%):	61%																										
Marked (50 - 75%):	16.1%																										
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Heat sensation	(9/12)																										
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Bulbar conjunctiva erythema	(1/12)																										
Redflushing	(5/12)																										
Schlager et al., 2016¹⁴																											
<p>One RCT identified from 2008 on adult patients with plaque psoriasis of the head and face:</p> <p><u>Tacrolimus (0.1%) ointment twice/day vs Pine Tar 5% ointment twice/day (n = 40)</u> Clearance RR (95% CI): 2.75 (1.05, 7.20) favours tacrolimus NNTB (95% CI): 3 (2, 15)</p>	<p><i>“The evaluation of tar preparations and other products, such as ciclopirox olamine, tacrolimus, dithranol and urea combination or steroids in combination with salicylic acid, was limited due to insufficient evidence.”</i> (pp. 47)</p>																										
Whitton et al., 2015⁴																											
<p>One RCT identified from 2009 on adult vitiligo patients:</p> <p><u>Tacrolimus (0.1%) ointment twice/day vs Pimecrolimus (1%) ointment twice/day (n = 25) (P = 0.226)</u> >75% repigmentation RR (95% CI): 2.15 (0.72, 6.48) >1 favours pimecrolimus</p>	<p><i>“The topical immunomodulator, tacrolimus, seems to be a reasonable alternative to topical corticosteroids, particularly on anatomical sites where there may be a higher risk of adverse effects with topical corticosteroids. Although clinical advice has usually been to exercise caution when combining topical immunomodulators with light therapies,</i></p>																										

Main Study Findings	Author's Conclusion
<p><u>Tacrolimus Adverse Events</u></p> <p>Burning sensation (9/12) Soreness (1/12) Pruritus (1/12) Conjunctiva erythema (1/12) Redflushing w/ alcohol (5/12)</p> <p><u>Pimecrolimus Adverse Events</u></p> <p>Soreness and erythema (2/13) Mild erythema (1/13) Intense erythema (1/13) Burning sensation (4/13) Intense lachrymation (1/13) Redflusing w/ alcohol (2/13)</p>	<p><i>due to the theoretical long-term risk of skin cancer, these combinations may have benefit if used under close medical supervision.” (pp. 27)</i></p>

Mason et al., 2013¹

<p>One single-blind RCT from 2006 on adult chronic plaque psoriasis patients:</p> <p><u>Tacrolimus (0.1%) ointment twice/day vs Calcipotriol (0.005%) ointment twice/day (n = 124) RD > 0 favours tacrolimus</u> IAGI RD (95% CI): -0.22 (-0.60, 0.16) PAGI RD (95% CI): -0.13 (-0.51, 0.24) Total withdrawals RD (95% CI): -0.13 (-0.25, -0.01) Withdrawals due to AEs RD (95% CI): 0.02 (-0.08, 0.11) Withdrawals due to treatment failure RD (95% CI): -0.02 (-0.07, 0.03) Adverse events (local) RD (95% CI): -0.19 (-0.37, -0.01) Adverse events (systemic) RD (95% CI): 0.0 (-0.04, 0.04)</p>	<p><i>“No significant difference was evident when calcipotriol was compared to tacrolimus ointment...” (pp.30)</i></p> <p><i>“We found the rate of total withdrawals was significantly lower for calcipotriol than for tacrolimus” (pp. 48)</i></p>
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CI = confidence interval; IAGI = Investigator's Assessment of Overall Global Improvement; NNTB = number needed to benefit; PAGI = Patient Assessment of Overall Global Improvement; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio/

Table 7: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusion
Silpa-Archa et al., 2016¹⁵	
<p><u>Repigmentation > 50% (n = 18 both groups)</u> Tacrolimus: 22% Mometasone: 33%</p> <p><u>Repigmentation > 75% (n = 18 both groups)</u> Tacrolimus: 11% Mometasone: 11%</p> <p><u>Repigmentation NONE (n = 18 both groups)</u> Tacrolimus: 17% Mometasone: 17%</p> <p><u>Repigmentation at 2 months (n = 18 both groups)</u> Tacrolimus: 17% Mometasone: 44%</p> <p>Tacrolimus vs Mometasone lesion repigmentation grading no statistically significant difference at six months (P = 0.13)</p>	<p><i>“As this is a pilot study, the limitation included the small number of participants. A larger group is essential to confirm the efficacy and safety of both agents for adult vitiligo. In conclusion, 0.1% tacrolimus ointment and 0.1% mometasone furoate cream are effective in the treatment of adult nonacral vitiligo; however, topical tacrolimus has fewer adverse effects.” (pp. 179)</i></p> <p><i>“Based on these results, mometasone appears to be an appropriate choice in patients for whom tacrolimus is unaffordable.” (pp. 179)</i></p>

Main Study Findings	Author's Conclusion
<p>Adverse events Telangiectasia (n = 18 both groups) (P < 0.03) Tacrolimus: 0% Mometasone: 33%</p> <p>Striae or skin atrophy (n = 18 both groups) Tacrolimus: 0% Mometasone: 0%</p> <p>Slight burning and stinging sensation (n = 18 both groups) Tacrolimus: 44% Mometasone: 28%</p>	
Park et al., 2016¹⁶	
<p>This study examined a patient population with an age range from 1 to 79 years. This study was included since multivariate analysis found no significant association with age and treatment outcome, (P = 0.52) however no power analysis was provided.</p> <p>Repigmentation > 50% (n/N (%)) (P < 0.001) Excimer laser: 30/100 (30%) Tacrolimus: 17/109 (15.6%) Excimer laser and Tacrolimus: 36/67 (54%)</p> <p>Multivariate analysis Treatment less than 6 months OR (95% CI) Age: 1.00 (0.97, 1.03), P = 0.83 Tacrolimus vs combination: 0.03 (0.01, 0.19), P < 0.001 Tacrolimus vs excimer laser: 0.20 (0.04, 1.09), P = 0.06</p> <p>Treatment 6 months or more OR (95% CI) Age: 1.00 (0.98, 1.02), P = 0.85 Tacrolimus vs combination: 0.44 (0.16, 1.19), P = 0.83 Tacrolimus vs excimer laser: 0.62 (0.25, 1.58), P = 0.83</p> <p>Multivariate analysis also suggested that sex and disease duration were not associated with treatment outcomes whereas the presence of genital lesions was associated with treatment failure.</p>	<p><i>"In this study, we found that short-term combination therapy of tacrolimus ointment plus excimer laser for up to 6 months' duration was associated with significantly better repigmentation than either therapy alone, but this superiority was not observed in patients treated for > 6 months. Our study population was relatively large (n = 276), and treatment duration was longer than that used in previous studies."</i> (pp. 239)</p>
Cavalié et al., 2015³	
<p>Some depigmentation (ITT, n = 72 lesions) (P = 0.059) Tacrolimus: 26.8% Placebo: 48.4%</p> <p>Some depigmentation (PP, n = 56 lesions) (P = 0.0075) Tacrolimus: 9.7% Placebo: 40.0%</p> <p>PGA score demonstrated (P = 0.0053) Depigmentation Tacrolimus: 10.4% Placebo: 48.2%</p>	<p><i>"Our results show that a maintenance treatment using twice weekly applications of tacrolimus 0.1% can reduce the recurrences of previously repigmented vitiligo lesions."</i> (pp. 972)</p> <p><i>"These results have a strong implication in terms of daily care of vitiligo patients. Further studies should determine the optimal topical therapy and schedule of applications along with the duration of such a maintenance treatment."</i> (pp. 973)</p>

Main Study Findings	Author's Conclusion
<p><u>No change</u> Tacrolimus: 58.6% Placebo: 40.7%</p> <p><u>Repigmentation</u> Tacrolimus: 31% Placebo: 11.1%</p> <p><u>QoL improvements (P = 0.6112)</u> Tacrolimus: 4.79 ± 3.58 to 3.54 ± 2.91 Placebo: 6.48 ± 2.80 to 4.59 ± 3.53</p> <p><u>All withdrawals were not treatment related</u></p>	

CI = confidence interval; ITT = intention-to-treat; OR = odds ratio; PGA = Physical Global Assessment; PP = per protocol.