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EXPERT OPINION

Topical Tacrolimus in Vitiligo: Consensus Paper from the Pigmentary Disorders Society

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Background: Tacrolimus, a topical calcineurin inhibitor (TCI) with immunomodulatory effects, is considered a viable treatment option for vitiligo. A consensus building exercise was undertaken to determine the role and clinical utility of topical tacrolimus in the management of vitiligo using input from experts in the field of dermatology.

Methods: Seventeen experts collaborated to create consensus statements using a modified Delphi methodology. A questionnaire on effectiveness, safety and utility of topical tacrolimus in different types of vitiligo, duration, frequency, monotherapy and combination and other aspects was shared, and a concordance rate of 75% was preset to have consensus. A physical meeting was conducted to discuss statements, which did not achieve consensus.

Results: Amongst 34 statements derived from round one, consensus was not achieved for 9 statements. In the second round, consensus was achieved for 2/9 statements, hence in the physical meeting, discussion was done to reframe the remaining seven statements. Apart from these 34 statements, questions pertaining to "Vitiligo: types and presentation in clinical practice", where consensus was not intended, are presented as descriptive statements.

Conclusion: Topical tacrolimus ointment has a favorable risk benefit profile to be used as one of the first-line agents for vitiligo. Combination of topical tacrolimus and narrow band Ultraviolet-B (NBUVB) was recommended as an effective treatment for non-segmental vitiligo. Recommended frequency of application was once or twice daily for optimal results. Apart from a transient burning sensation, topical tacrolimus has a favorable safety profile.

Keywords: topical calcineurin inhibitor, immunomodulatory, non-segmental vitiligo, depigmenting, autoimmune, autoreactive T cells, tacrolimus

Introduction

Vitiligo is a common depigmenting skin disorder affecting 0.004–2.28% of the world population with the reported prevalence in India between 0.25% and 4%.[1,2] It is characterised by macules and patches of depigmentation and is often associated with low self-esteem and social stigma. Melanocyte dysfunction with concurrent autoimmunity are purported to be important in the pathogenesis.[3,4] An immunologic imbalance represented by anti-melanocyte antibodies and autoreactive T cells causing cellular damage, is a well-established argument.[5,6]

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The management approach in vitiligo is often complex.[7] Topical medications (ie, corticosteroids and calcineurin inhibitors) along with phototherapy remain the mainstay of treatment.[8] However, with the recent development on the interferon-gamma (IFN-γ) signaling axis in vitiligo, numerous clinical studies with Janus kinase (JAK) inhibitors have recently demonstrated promising efficacy in vitiligo.[9] Surgical therapies and lasers are also available; however, none of these procedures consistently yield conclusive and satisfying outcomes in all patients.[10]

Topical calcineurin inhibitors (TCIs), initially developed to treat atopic dermatitis, have replaced long-term use of corticosteroids.[11] These medications attach to an intracellular protein known as (FK binding protein FKBP), which has an immunosuppressive effect on leucocytes and mast cells and stops the transcription of pro-inflammatory cytokines. Tacrolimus, being a member of this group, is available as an ointment formulation at two strengths 0.1% and 0.03% and is commonly used in the treatment of eczema.[11] Given its immunomodulatory actions, it was considered as a viable treatment for vitiligo.[12] Tacrolimus has been demonstrated to be quite beneficial for repigmentation in non-segmental vitiligo but is less effective for segmental and acrofacial disease.[13]

Throughout the last decade, TCIs have been considered a reasonable treatment for vitiligo, although its use remains off-label due to the lack of robust evidence coming from long-term comparative studies or large and adequately controlled RCTs. However, off-label prescribing is a common practice in medicine in general, and in dermatology in particular.[14–16]

Given the wide applicability of TCIs according to their mode of action and their narrow-approved indications for usage, a consensus building exercise was planned with the purpose of determining the role and clinical utility of topical tacrolimus in the management of vitiligo using the input from experts in the field of dermatology.

Materials and Methods

Seventeen experts in the field of clinical dermatology from the Pigmentary Disorders Society (PDS) collaborated to create consensus statements using a modified Delphi methodology. Pigmentary Disorders Society is an international society, having mostly members from India, as it is based out in India but also members from South Asia, Asia and advisors from different parts of the world. Hence, most studies are done after discussion and taking suggestions from members from different countries.

The expert panel for this consensus was composed of dermatologists with more than 15 years of expertise in their particular specialty and at least 10 years of experience using topical tacrolimus for vitiligo. A Google doc link was used to send a questionnaire with multiple choice type questions (majority) and a few open-ended questions, including the safety and effectiveness of topical tacrolimus in treating vitiligo, its use in treating different types of vitiligo, the effectiveness of different tacrolimus strengths, how often and for what duration they should be prescribed, and the overall experience of experts with topical tacrolimus.

The panellists were expected to respond to these questions within two weeks. A target concordance rate of >75% was set to reach a consensus for each question, and based on the answers received, consensus statements were framed. A physical meeting was held to review these statements and questions for which consensus had not been reached after two rounds of the Delphi technique, such as, those pertaining to the effectiveness of topical tacrolimus as monotherapy and its frequency of application as well as response rate. Three rounds of questionnaire-based conversations centred on the various facets of topical tacrolimus use in vitiligo were completed. Where appropriate, the panellists were required to agree, disagree, and express their perspectives regarding the questions. Figure 1 outlines the procedures that were used to create the consensus statements.

Results

A total of 34 statements were developed for the first Delphi round. Of these 34 statements, consensus was not achieved for 9 statements. In the second round, consensus was achieved for 2/9 statements, hence in the physical meeting, discussion was done on rest 7 statements which were reframed.

Other than these statements, questions pertaining to “Vitiligo: types and presentation in clinical practice”, where consensus was not intended, were also asked and are presented in the form of descriptive statements under Section 1.

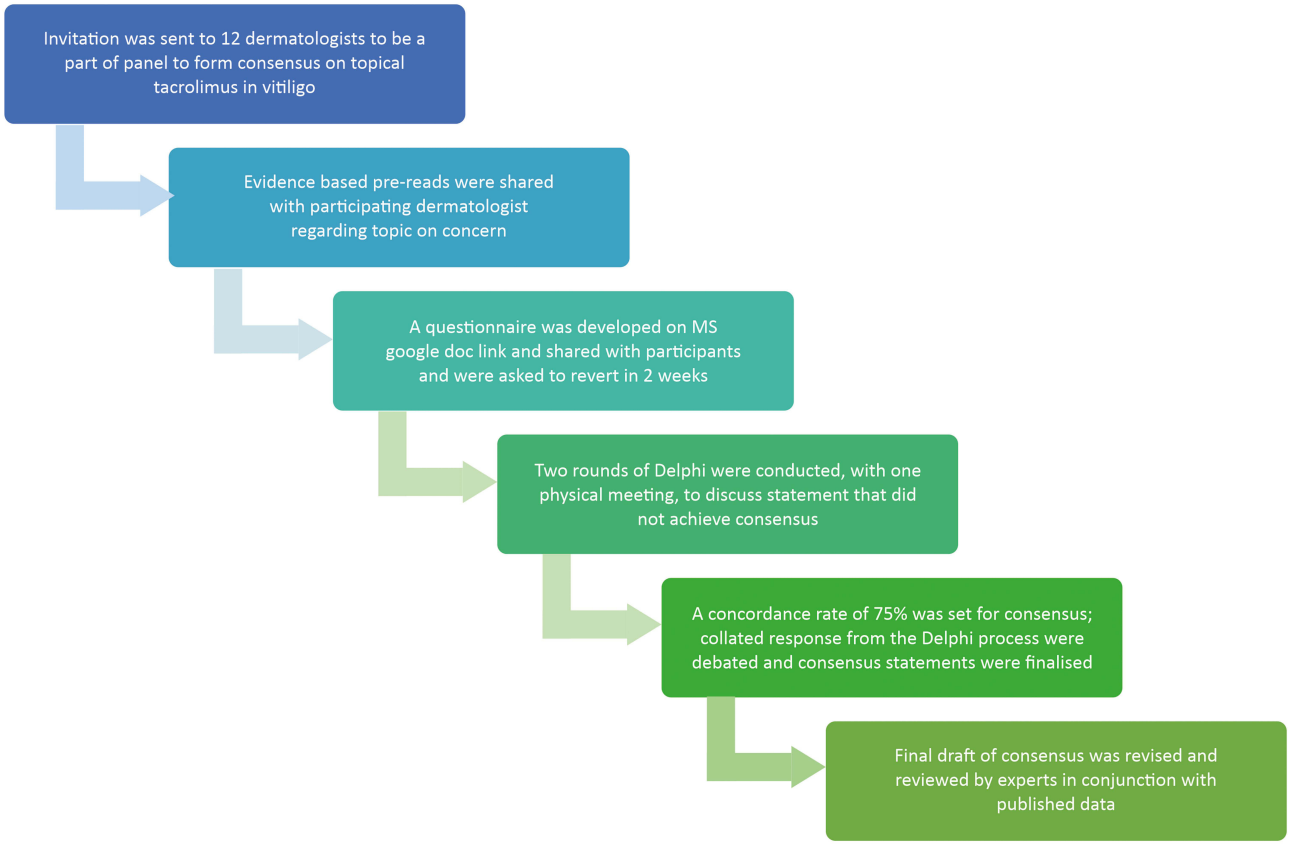

Figure 1 Methodology to derive consensus statements.

Section 2 includes the different aspects pertaining to the role of topical tacrolimus in vitiligo management as shown in Table 1.

Section 1

Vitiligo: Types and Presentation in Clinical Practice

All the experts agreed that >10 vitiligo patients are seen in a month with the most common age of presentation being 21–50 years in their clinical practice. Less than 10% of the vitiligo patients had a family history or a history of vitiligo in any of their first degree relatives. Of the total vitiligo patients encountered during in practice, majority of these present with non-segmental vitiligo with a mild to moderate disease, ie, affected body surface area (BSA) 10–30%. Less than 30% vitiligo patients have a limited disease (affected BSA up to 2–3%), while a minor proportion of patients (<10%) have severe disease (affected BSA >30%). About 10–30% of vitiligo patients have a rapidly progressive or an unstable vitiligo.

Section 2

Consensus statements derived by experts are categorized into 7 domains viz. a. preferred treatment interventions in vitiligo, b. response rate to topical tacrolimus as monotherapy, c. response rate to topical tacrolimus as combination therapy, d. strength of topical tacrolimus preferred in clinical practice, e. frequency, timing and duration of application, f. repigmentation and g. safety and tolerability and are described in detail in Table 1.

Table 1 Role of Topical Tacrolimus in the Management of Vitiligo

Serial No	Section	Statement	Consensus (Round 1)	Consensus (Round 2)	Reframed Statement
1	**Preferred treatment interventions in vitiligo**	Topical immunosuppressants/immunomodulators are among the most preferred initial treatment intervention for vitiligo	Consensus		
2		Preferred topical intervention is anti-inflammatory agents ie potent steroids with or without TCI	Consensus		
3		Topical tacrolimus is prescribed either as monotherapy or as a part of combination for the management of vitiligo in >50% patients	Consensus		
4		Topical tacrolimus can be prescribed as occlusive therapy	No consensus	No Consensus	Topical tacrolimus is not preferred to be prescribed as occlusive therapy
5	**Response rate to Topical tacrolimus as monotherapy**	Topical tacrolimus has a favourable risk-benefit profile to be considered as monotherapy for limited disease in adults and children	Consensus		
6		0.1% topical tacrolimus monotherapy is preferred as a first line therapy for non-segmental vitiligo affecting up to 10% BSA in clinical practice	No consensus	Consensus	
7		The response with 0.1% topical tacrolimus monotherapy in patients with non-segmental vitiligo affecting up to 10% BSA is satisfactory	No consensus	Consensus	
8		10 to 30% patients treated with topical tacrolimus experience recurrence within a year	Consensus		

9	**Response rate to Topical tacrolimus as combination therapy**	Topical tacrolimus is prescribed most frequently as a part of combination with both systemic and other topical therapies	Consensus		
10		Topical tacrolimus is prescribed most frequently in combination with topical steroids and/or phototherapy	Consensus		
11		>75% regimentation observed in practice with combination regimes involving topical tacrolimus	Consensus		
12		Best combination for achieving >75% regimentation: topical tacrolimus plus NBUVB	Consensus		
13		Combination therapy with topical tacrolimus rated superior as compared to monotherapy	Consensus		
14		In non-segmental vitiligo affecting up to 10–40% BSA, topical tacrolimus is used concurrently in combination with phototherapy throughout the duration of therapy.	No consensus	No consensus	In non-segmental vitiligo affecting up to 10–40% BSA, topical tacrolimus can be used concurrently or intermittently in combination with phototherapy over limited body parts throughout the duration of therapy.
15		>50% repigmentation could be achieved with the above combination	Consensus		
16	**Strength of topical tacrolimus preferred in clinical practice**	The prescribed strength for topical tacrolimus in practice is mostly* 0.1% (*mostly: ≥90%)	Consensus		
17		Age group for which 0.03% topical tacrolimus is prescribed is below 2 years	Consensus		
18		Tacrolimus 0.1% solution might be useful in hairy areas	Consensus		
19	**Frequency, timing and duration of application**	Topical tacrolimus is prescribed as a twice daily application	No consensus	No consensus	Topical Tacrolimus can be prescribed as once daily or twice daily but better results are seen with twice daily application
20		Topical tacrolimus could be prescribed in a maximum continuous duration up to 6 months.	Consensus		

(*Continued*)

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Table 1 (Continued).

Serial No	Section	Statement	Consensus (Round 1)	Consensus (Round 2)	Reframed Statement
21	**Repigmentation**	Site that responds the most/best to topical tacrolimus: Face	Consensus		
22		Peak response of repigmentation (>50%) with topical tacrolimus seen at 3–6 months	Consensus		
23		Repigmentation is minimal/difficult with topical tacrolimus on palms and soles and finger-tips	Consensus		
24		Topical tacrolimus can be prescribed as maintenance (to prevent depigmentation in previously repigmented lesions)	No consensus	No consensus	Topical tacrolimus can be prescribed as maintenance therapy, however physician discretion is warranted
25		Topical tacrolimus is tapered over a few weeks and discontinued thereafter on achieving a desired treatment outcome	Consensus		
26		Topical tacrolimus use in mucosal vitiligo results in mild improvement	Consensus		
27		Good response with topical tacrolimus considering the cost benefit ratio	Consensus		
28		<10% patients refractory to other topical immunosuppressants/ local phototherapy/ laser would respond to topical tacrolimus	Consensus		
29		Repigmentation with topical tacrolimus 0.1% is comparable to mid to super potent TCS	No consensus	No consensus	Considering 50% repigmentation rates, super-potent TCS demonstrate better efficacy than TCI. However, repigmentation efficacy of TCI is comparable to and safer than mid-potent TCS.
30		Repigmentation with topical tacrolimus 0.1% in segmental vitiligo is satisfactory-	No consensus	No consensus	Only one third of the segmental vitiligo patients seen in clinical practice respond satisfactorily to topical tacrolimus.
31	**Safety and Tolerability**	Topical tacrolimus can be prescribed in vitiligo patients with larger BSA affected	No consensus	No consensus	Although topical tacrolimus has very low systemic absorption, compliance and cost factors need to be considered in patients with larger BSA affected.
32		Tolerability of topical tacrolimus is rated good	Consensus		
33		Transient burning/tingling is the commonest side effect encountered with topical tacrolimus	Consensus		
34		None of the SAEs – malignancy or risk of serious infections were noted in practice with the use of topical tacrolimus	Consensus		

Discussion

Achromic patches on the skin that are caused by melanocyte loss in the epidermis and hair follicles are the hallmarks of vitiligo. Disease onset is mostly in childhood and puberty, however it can manifest at any age in both sexes.[17] It has a significant impact on the patients' quality of life.[18] None of the therapeutic options are completely gratifying, either because of the unexpected progression and lengthy therapy or due to the side effects and challenging practical aspects of applying topical medications.[19,20]

Treatment methods are selected for each patient individually based on the severity and extent of the condition, the activity of the disease (stable versus progressive disease), the patient's preferences (including cost and accessibility) and the evaluation of the patient's response. Low-dose oral glucocorticoids and phototherapy can help stabilise an illness that is rapidly progressing. Targeted phototherapy, surgical therapy, and topical therapies such as, TCS and TCI are available treatment options to aid in repigmentation. In topical, TCS and TCI are the most commonly used medications.[21] Experts also opined on a similar line. In addition, experts were of the opinion that TCIs are used in >50% of vitiligo patients seen in their practice, either as monotherapy or in combination. Though long-term treatment with topical tacrolimus as occlusive therapy was found to be effective and safe in vitiligo,[22] experts were against the use of tacrolimus as occlusive therapy, especially when larger areas are being treated.

Topical Tacrolimus: Strength, Frequency, Duration and Repigmentation

Topical tacrolimus is approved in two strengths; 0.1% and 0.03%. Tacrolimus of both strengths (0.1% and 0.03%) is approved for use in adults, while only 0.03% is approved to be used in paediatric patients 2–15 years of age for atopic eczema.[23] However, there was an agreement regarding the use of topical tacrolimus in vitiligo being an off-label indication.

A twice daily application of topical tacrolimus is recommended in the management of atopic dermatitis. In vitiligo as well, there are several studies where tacrolimus was studied as twice daily application.[24–28] In one of the studies, tacrolimus twice daily application was compared with once daily which concluded better repigmentation rate with twice daily application.[28] In case of paediatric vitiligo, 85% of the children placed on twice-daily tacrolimus regimen responded in contrast to only 55% of the children who used the ointment once daily.[26]

In an open-label study of 6 months' duration of 0.1% tacrolimus twice daily application, a greater than 75% repigmentation was obtained in 68% of the facial and/or neck lesions compared to only 13% of trunk lesions and 6% of upper extremity lesions.[24] A 12-week evaluation of 22 children treated with twice daily tacrolimus 0.03% in an Indian study, revealed full repigmentation in 50% of the children.[27] In a different study, 57 children with various types of vitiligo were retrospectively evaluated for the efficacy of 0.03% or 0.1% tacrolimus ointment treated either once or twice daily for 3 months. Greater than 75% repigmentation was seen in 47% of the children with involvement in head and/or neck and in 25% of children with trunk and/or extremity involvement. Only 55% of the children who used the ointment once a day responded, compared to 85% of the children who were put on the twice-daily schedule.[26] In a study by Tanghetti, twice-daily applications of tacrolimus ointment 0.1% for up to 9 months were well tolerated with the onset of response by 6 to 8 weeks of treatment initiation.[29] Another study on adult patients with facial vitiligo found that twice-daily tacrolimus 0.1% ointment was more effective than a control group in both the interventions and follow-up periods of 24 weeks.[30]

One study showed that following successful repigmentation, maintenance therapy with TCIs prevented the recurrence of vitiligo.[31] For the management of atopic dermatitis, proactive treatment with TCIs has been advised in order to stop future flare-ups.[32] TCIs also appear to be useful in preventing the development of new depigmented patches in non-segmental vitiligo.[33] In one study involving segmental vitiligo patients, topical tacrolimus and fluticasone propionate, both produced variable but unsatisfactory repigmentation.[34] In another clinical study by Kumar et al, tacrolimus 0.1% ointment application showed effectiveness in preventing the appearance of new lesions in unstable acral vitiligo and hastened the repigmentation when applied to both lesional and perilesional skin in vitiligo.[35]

In the present survey, no consensus was achieved regarding the frequency of application; where 63% of experts voted for once daily application and 27% for twice daily application, mainly due to poor tolerability when used twice daily.

There was positive consensus regarding peak response to repigmentation achieved with topical tacrolimus at 3–6 months. As per the experts, topical tacrolimus results in good repigmentation in facial vitiligo as compared to vitiligo on other body areas such as palms, soles, mucosa and finger-tips where repigmentation is found to be minimal. Repigmentation in non-segmental vitiligo is good considering the cost–benefit ratio for topical tacrolimus as per experts' opinion. In addition, owing to the scarcity of clinical data, no consensus could be achieved on the role of tacrolimus as maintenance therapy. Recommendations are summarized as Experts' comments in Table 2.

Tacrolimus as Monotherapy or Combination Therapy

Topical tacrolimus may be used alone or in conjunction with other treatments for vitiligo. In a meta-analysis by Lee et al, 55% of patients showed a modest response (25% repigmentation) after a median treatment period of 3 months with tacrolimus monotherapy.[33] Children showed repigmentation rates of 25% in 66.4% of cases and 75% in 31.7% of cases. The face and neck outperformed other sites in terms of response, with 73.1% of patients achieving at least a modest response, compared to other body area regions where no such response was observed.[36]

As combination therapy, there are many studies which compared different combinations. Tacrolimus in combination with narrowband UVB (NB-UVB) and fractional laser was found better than monotherapy. But there was no difference between excimer laser and tacrolimus combination therapy versus excimer laser alone.[33]

Topical tacrolimus in combination with phototherapy had better treatment outcomes than either of the monotherapy treatments, with at least a moderate response attained in 89.5% of patients. The trunk and extremities, which are protected from the sun, is where the difference between tacrolimus monotherapy and tacrolimus combination with phototherapy was most noticeable in terms of treatment response.[33] Vitiligo may be treated by modulating the immune response and stimulating melanocytes through UV exposure.[37] Theoretically, this synergism can be explained by UV-B-induced endothelin secretion from keratinocytes and tacrolimus-induced endothelin B receptor expression in melanoblasts.[38] Recommendations are summarized as Experts' comments in Table 3.

Topical Tacrolimus Vis a Vis Topical Corticosteroids

Both TCI and TCS are widely used and are regarded as first-line agents for limited forms of vitiligo in guidelines.[10,39] According to one meta-analysis, both TCI and TCS achieved equivalent success (≥50% or ≥75% repigmentation), with a significant fraction of the paediatric population achieving a higher treatment response compared to the overall population.[39] On comparing 50% repigmentation rates, super-potent TCS demonstrated better efficacy than TCI. However, when there are concerns about the alleged negative consequences of long-term potent TCS use, TCI can be a useful and secure substitute for TCS.[39] Recommendations are summarized as Experts' comments in Table 4.

Safety

Despite being highly lipophilic, tacrolimus diffusion into the systemic circulation was minimal, with systemic exposure to tacrolimus being 750 and 1800 times lower than that observed in the skin at 24 h after the first and last applications, respectively.[40] Numerous studies had evaluated the systemic absorption of topical tacrolimus and found low levels of

Table 2 Topical Tacrolimus: Strength, Frequency, Duration and Repigmentation

Topical tacrolimus 0.1% should be used in adult vitiligo while 0.03% can be used in paediatric vitiligo
Topical tacrolimus can be prescribed as once daily or twice daily but better results are seen with twice daily application with a peak response of repigmentation (>50%) by 3–6 months
Topical tacrolimus works better in facial vitiligo as compared to other body areas like hands/feet or trunk
It can be prescribed as maintenance therapy, but physician discretion is warranted in lieu of duration
Topical tacrolimus is tapered over a few weeks and discontinued thereafter on achieving a desired treatment outcome
<10% patients refractory to other topical immunosuppressant/local phototherapy/laser would respond to topical tacrolimus

Table 3 Topical Tacrolimus as Monotherapy or Combination Therapy

Topical tacrolimus has a favorable risk-benefit profile to be considered as monotherapy for limited disease in adults and children and is preferred as one of the first line therapy for non-segmental vitiligo affecting up to 10% BSA in practice
<50% of patients with non-segmental vitiligo affecting up to 10% BSA respond to tacrolimus 0.1% monotherapy with a recurrence in 10–30% of the patients within a year
Topical tacrolimus is prescribed most frequently as a part of combination with both systemic and other topical therapies and phototherapy
Combination therapy with topical tacrolimus rated superior as compared to monotherapy
Topical tacrolimus and NBUVB is an ideal combination and >75% regimentation observed with this combination in practice
In non-segmental vitiligo affecting up to 10–40% BSA, satisfactory repigmentation (>50%) could be achieved with combination therapies involving topical tacrolimus

Table 4 Topical Tacrolimus Vis a Vis Topical Corticosteroids

Results of repigmentation achieved on comparing TCS and TCI are variable in current practice, more studies especially in Asian/Indian population would be required to arrive at a definitive conclusion.

Table 5 Safety and Tolerability of Topical Tacrolimus

Safety and tolerability of topical tacrolimus is good, although irritation and pruritus at application site are the commonest side effects.
Risk of malignancy or serious infections was not noted with long term use of topical tacrolimus in practice.

tacrolimus in the blood.[41,42] Undre et al in his study concluded minimal systemic absorption after topical application of tacrolimus in patients with atopic dermatitis.[40]

Treatment with topical tacrolimus is generally safe and free from major local side effects. No serious adverse events occurred that required treatment to be stopped. British guidelines suggest that TCIs may be considered for adults and children with vitiligo as an alternative to TCS, given their better short-term safety profile.[43]

The currently available evidence indicates the low risk of serious harm with TCI.[44] In clinical studies with TCIs in adult and paediatric populations, skin burning (up to 58% of cases), pruritus (46%), and erythema (28%) were the most frequently reported adverse events (AEs).[45,46] These AEs, which were more frequently observed in adults than in children, were brief and resolved within a week of treatment as the skin barrier strengthened and the AD lesions healed.[43] By combining TCIs with a moisturiser in a 1:1 ratio, precooling the TCI for 15 to 20 minutes before application and utilising emollients to treat AD, skin burning can be reduced.[47–51]

Svensson et al found no statistical difference between TCS and TCI in terms of safety in his systematic review.[48] Moreover, TCI is preferred over TCS since long-term use of TCS is associated with AEs including skin atrophy, striae and telangiectasia.[44,48] A systematic review by Hanna et al concluded that the increased risk of malignancies with TCI as theoretical.[44] A multicenter retrospective cohort study of 25,694 vitiligo patients, no association of lymphoma or skin cancer was reported with the use of topical calcineurin inhibitors, either as monotherapy or in combination with phototherapy, in vitiligo.[52] Recommendations are summarized as Experts' comments in Table 5.

Conclusion (Summary Capsule)

The expert panel from PDS opined that topical tacrolimus ointment has a favorable risk–benefit profile and could be effectively used as one of the first-line agents for the management of vitiligo in clinical practice. For limited or localized (mild–moderate) disease up to 30% of BSA involvement, topical 0.1% tacrolimus can be used as monotherapy or in combination with other topical therapy like TCS and for severe forms of disease or extensive involvement (>30% BSA), it can be used in combination with phototherapy (NBUVB), systemic immunosuppressant and other topical therapies used over

limited areas as may be deemed necessary. Experts favored the combination of topical tacrolimus and NBUVB therapy as an effective treatment modality for non-segmental vitiligo, and this combination was successful in achieving repigmentation rates as high as or >75%. Experts recommended the frequency of application as once or twice daily for optimal results and although a transient burning sensation was commonly experienced by patients with topical tacrolimus, its use was not associated with any serious side effects and did not lead to treatment discontinuation. Overall, with the satisfactory repigmentation seen with 0.1% tacrolimus and without any serious safety concerns as compared to long-term concerns associated with the use of TCS, topical tacrolimus could be a suitable agent for vitiligo management, a condition with limited approved therapies in practice.

Ethics Approval/IRB Approval

As per the Indian Council for Medical Research (ICMR) any research on "educational practices such as instructional strategies or effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods", can be exempted from ethics committee review. As per this statement, there is no need for ethics committee approval in the case of our manuscript. The work was conducted according to the Declaration of the Helsinki Principles.

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The authors report no conflicts of interest in this work.

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