"COMPARISON OF EFFICACY OF TOPICAL JANUS KINASE INHIBITOR TOFACITINIB USED ALONE VERSUS USED IN COMBINATION WITH TARGETED NARROW-BAND ULTRAVIOLET B (EXCIMER) THERAPY"

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LIST OF ABBREVIATIONS

SrNo.	Abbreviation	Full form
1.	**UVA**	Ultra violet A
2.	**PUVA**	psoralens combined with ultra violet A
3.	**NBUVB**	Narrowband ultraviolet-B
4.	**IFN-γ**	Interferon-gamma
5.	**JAK**	Janus Kinase
6.	**SV**	Segmental Vitiligo
7.	**NSV**	Non-Segmental Vitiligo
8.	**BSA**	Body surface area
9.	**DNA**	Deoxy-riboneuclic acid
10.	**ROS**	Reactive oxygen species
11.	**UPR**	Unfolded protein response
12.	**DC**	Dendritic cells
13.	**TCs**	Topical corticosteroids
14.	**IL**	Interleukin
15.	**TNF-α**	Tumor Necrosis factor-α
16.	**5-FU**	5-Fluorouracil
17.	**MTX**	Methotrexate
18.	**PDE**	Phosphodiesterases
19.	**cAMP**	Cyclic Adenosine Monophosphate
20.	**STAT**	Signal transducer and activator of transcription
21.	**DMARD**	Disease modifying anti-rheumatic drugs

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ABSTRACT

BACKGROUND

A chronic skin disorder which occurs due to loss of melanocytes and manifests with patches of depigmentation is categorized as vitiligo. Despite various treatment modalities, including corticosteroids and phototherapy, no definitive cure exists. Recent advances highlight that Janus Kinase inhibitors such as Tofacitinib play a role in regulating the immune mechanism associated with the pathogenesis of vitiligo. Hence, this study was undertaken. to compare the effectiveness of topical Tofacitinib alone versus its combination with narrowband ultraviolet B (NBUVB) therapy.

AIMS AND OBJECTIVES

To compare the effectiveness of topical JAK inhibitor (Tofacitinib) alone versus used along with concomitant phototherapy on de-pigmented lesions of vitiligo and to determine the effect of topical JAK inhibitor (Tofacitinib) on pigmentation in vitiligo lesions.

MATERIALS AND METHODS

A nonrandomized, interventional, open-label study was done over one year at a dermatology outpatient department. A total of 34 vitiligo patients were recruited. Two depigmented patches were selected per patient: one treated with topical Tofacitinib (2%) alone and the other with Tofacitinib combined with Excimer. Treatment outcomes were evaluated by using the vitiligo area scoring index, dermoscopic evaluation and serial photography at baseline, 4, 8, and 12 weeks. Statistical analysis was performed using repeated measures ANOVA.

RESULTS

The study observed a reduction in vitiligo area scoring index significantly over 12 weeks in both treatment categories . The combination therapy (topical Tofacitinib+Excimer) showed a

superior mean improvement in VASI (74.07%) compared to Tofacitinib monotherapy (62.08%). The Difference in vitiligo area scoring index reduction between both the categories was significant statistically at the 8th week and 12th week with a p-value of 0.001 and 0.013respectively. Dermoscopic assessment revealed enhanced peri-follicular pigmentation and improved pigment network restoration in the combination group. Notably, treatment response was more pronounced in sun-exposed areas, with reduced efficacy in acral and bony sites. Mild transient adverse effects, including erythema (6 cases), post-inflammatory hyperpigmentation (2 cases), and desquamation (1 case), were observed only in the combination group.

CONCLUSION

Topical Tofacitinib is one of the useful modes of treatment modality for vitiligo showing enhanced effectiveness when it is combined with NBUVB therapy. . Despite minor, transient adverse effects, combination therapy offers a promising approach for vitiligo management. Further large-scale studies are required to authenticate the study findings.

INTRODUCTION

Vitiligo is anacquired, chronic cutaneous conditionwitha progressive decline in melanocyte count, leading to the development of white patches representing reduced to absent pigmentation of the skin. This condition is reported in about 0.5% to 2% of the population worldwide and occurs across all ethnicities and age groups.[1] While vitiligo is not physically harmful and does not cause pain or irritation, its cosmetic impact can be profound, often leading to significant psychological distress, low self-esteem, anxiety, and depression.[2] The condition is particularly distressing for individuals with duskierskin tones, as seen in Indians, where the affected area appears more noticeably distinct from the unaffected areas. The stigma associated with the appearance of these white patches can reduce the quality of patient's life, and it can also be the cause of emotional stress.[2]

Several treatment options have been explored for vitiligo, aiming to halt disease progression and restore pigmentation. Therapies often used in clinical practice are corticosteroids, both topical and oral, psoralens combined with ultra violet A (UVA) therapy (PUVA), narrowband ultraviolet-B (NBUVB) therapy, topical calcineurin inhibitors, and Excimer laser therapy.[3] These treatments work through various mechanisms, such as modulating the immune response, stimulating melanocyte proliferation, or promoting melanocyte migration from surrounding skin and hair follicles. However, despite these available options, no single treatment has been proven to provide a complete and permanent cure for vitiligo.[3] Moreover, some therapies, such as long-term corticosteroid use, come with significant side effects, including skin thinning, striae formation, and adrenal suppression.[3]

Recent advancements in research have enabled the successful delineation of pathways which are pivotal in the pathogenetic mechanism of vitiligo, especially the role of interferon-gamma (IFN-γ).[4] . In vitiligo, CD8+ T lymphocytes target the melanocytes and destroy them; hence

it is categorized as an autoimmune disorder. A pro-inflammatory cytokine is releasedin response to melanocyte-specific antigen presentation, triggering a cascade of immune reactions.[4] IFN gamma activates the Janus Kinase/signal transducer and activator of the transcription pathway, which finally leads to melanocyte apoptosis and, via a positive feedback loop, recruits more self-reactive T cells, further exacerbating disease.[1] This process creates a vicious cycle, where continuous melanocyte destruction results in expanding depigmented patches on the skin. Janus Kinase (JAK) inhibitors are emerged as a promising treatment option due to their involvement in the pathogenetic mechanism.[1, 4] Oral as well as topical formulations of it are tried for their potential in halting disease progression and promoting repigmentation. Among them, Tofacitinib, an oral JAK inhibitor, has demonstrated notable efficacy in re-pigmenting vitiligo lesions. However, systemic administration of Tofacitinib has been linked to significant adverse effects, including pancytopenia, malignancies, weight gain, and lipid profile alterations.[4-6] Due to these concerns, topical JAK inhibitors are being explored as a safer alternative, as they offer targeted treatment with potentially fewer systemic side effects.[7]

While some studies have reported successful repigmentation with topical Tofacitinib as monotherapy,[6] others suggest that its effectiveness is enhanced when combined with phototherapy.[5] Hence this study was undertaken to compare the effectiveness of topical Tofacitinib alone versus combined with phototherapy in providing valuable insights into its potential role in vitiligo management.

AIMS AND OBJECTIVES

1. To compare the effectiveness of topical JAK inhibitor (Tofacitinib) alone versus used along with concomitant phototherapy on de-pigmented lesions of vitiligo.
2. Determine the effect of topical JAK inhibitor (Tofacitinib) on pigmentation in vitiligo lesions.

REVIEW OF LITERATURE

The skin doesn't act as a protective barrier only but it also regulates body temperature, produces hormones, and provides insulation. It also contributes to thermoregulation and maintaining overall homeostasis.[8] One of the essential functions of the skin is to facilitate human communication, enabling humans to achieve personal and societal goals. It plays a vital role in interpersonal interactions by expressing beauty, capturing attention, and contributing to the formation and expression of self-identity.[9] The perception of physical imperfections in the color or texture of skin varies across cultures. In Indian society, for instance, the presence of vitiligo is considered a social taboo and can sometimes lead to the annulment of a marriage agreement.[10] The skin primarily consists of two layers: the epidermis and the dermis. The epidermis primarily has four cell types: the keratinocytes, which are the predominant cells present; the Merkel cells, which are the sensory cells; the Langerhans cells, which are the immune cells of the skin; and lastly, the melanocytes, which are responsible for its pigment; production.[8] Human skin color is influenced by several pigments which are produced by the melanocytes. Melanin is the most significant of these, responsible for the brown color of the skin and hair.[10]

Skin pigmentation

Major variants of skin pigmentations are as follows:[11]

1. Eumelanin: These insoluble pigments appear in shades of brown or black and contain nitrogen.
2. Phaeomelanin: Ranging from red-yellow to brown and contains both nitrogen and sulfur.
3. Trichochromes: These are considered by some authors as a form of phaeomelanin and are responsible for red color, which contains sulfur.

The regulation of pigmentation is a complex process influenced by multiple factors that govern the development, diversity, regeneration, and ageingof melanocytes and their precursors. Additionally, it involves mechanisms that determine the structure of melanosomes as well as melanin synthesis and transport of melanosomes which is. necessary for pigmentation of surrounding keratinocytes. [10]

Vitiligo

Vitiligo is a commonestdefect of pigment-producing cells of the skin, with an incidence of 0.25–2%.It mainly affects young adults.[12] It is a common form of localized de- or hypo-pigmentation. It is a condition that develops over time due to the gradual loss of pigment forming cells, i.e. melanocytes, and it presents as whitish discolouration of skin .[13] Vitiligo has a profound effect on the social and mental condition of the patients especially in individuals with darker Indian skin tones, where the contrast of white lesions is more pronounced.[11]

HISTORY

The condition was initially described over 1,500 years BC.[14] One of the earliest references to vitiligo appears in the *Charaka Samhita* (100 AD), an ancient Ayurvedic medical text, where the condition is described as *svitra* ("whiteness").[15]

EPIDEMIOLOGY

Vitiligo is frequently overlooked in public health discussions.[16] It is one of the most prevalent skin disorders associated with reduced or absent pigmentation, with a prevalence ranging from 0.25% to as high as 4% in the Indian subcontinent.[17, 18] Although females are more often seeking medical attention due to a greater social impact, vitiligo affects both sexes

indiscriminately.[17]

Vitiligo patients can be categorized into two distinct groups. In group 1, lesion starts before the age of 12 years and in group two after the age of 12 years. [19]

CLASSIFICATION

An international consensus, which sat in 2011, redefined vitiligo classification, distinguishing the segmental form from all other variants and reserve usage of the term "vitiligo" exclusively for non-segmental forms. The following classification was proposed:[20]

1. Segmental Vitiligo (SV): Affecting only a specific body region, which included focal (one or few isolated patch/s over a specific area), Uni-, Bi- or multisegmental forms (involving one, two or few dermatomes respectively)
2. Non-Segmental Vitiligo (NSV): Encompasses various subtypes, including hard-to-treat forms like those involving mucosa and acro-facial regions, those with extensive involvement like generalized and universal variants, along with rare variants such as leukoderma punctata, hypochromic vitiligo, and follicular vitiligo.
3. Mixed Type (NSV + SV): Represents cases where both segmental and non-segmental patterns coexist in the same individual.
4. Unclassified: Includes vitiligo presentations that do not clearly fall into the established categories.

A latent class analysis study identified two distinct phenotypes of NSV based on the age at onset, as discussed previously. Group one isoftenrelatedwith family history of canities and halo nevi. Group two presents with onset at a much later age and is predominantly marked by acro-facial depigmented patches.[21, 22]

Lerner et al.[23] classified vitiligo into 3 groups, namely:

1. Segmental form, which presents with partial, focal or localized hypo- or de-pigmented patches representing a dermatomal distribution.
2. Vitiligo vulgaris is a generalized variant, a complete or universal form affecting all or nearly all parts of the axial and peripheral body.

In the Vitiligo Global Issues Consensus Conference – 2012,[24] they came up with a classification based on the staging of the extent of the disease as follows:

1. less than10% BSA involved denotes a limited disease
2. 10-25% BSA involved represents a moderate disease
3. 26-50% BSA involvement signifies a moderate to severe form
4. More than50% BSA involvement is deemed as a severe form of the disease

Koga and Tango,[25] based on sweat stimulation studies, classified vitiligo into two types:

1. Type A, which does not show a dermatomal distribution, is believed to have an autoimmune origin and has shown responsiveness to steroid treatment.
2. Type B, wherein the disease develops along particular singular or multiple dermatomes. When there is an association with sympathetic dysfunctions, response to nialamide therapy is noted.

PATHOGENESIS:

1. *Genetic Background*

Vitiligo is recognized as a multi-factorial disorder, influenced by multiple susceptibility genes that contribute to its development.[17] Some of the involved genes are listed below with other conditions that are reported to be associated with:

Gene	Other associated conditions
GPX1	Dermatological: Alopecia areata and Psoriasis Non-dermatological: Diabetes Mellitus-II, Angina and Myocardial Infarction, Hypocortisolism
COMT	Dermatological: Atopic dermatitis and Psoriasis Non-dermatological: Schizophrenia, Alcoholism
DDR1	Ovarian cancer, malignant melanoma
GZMB	Thyroid disease
PTPN22	Dermatological: Psoriasis Non-Dermatological: Juvenile Diabetes Mellitus, Endocrine disorders like Hypocortisolism and Graves disease, ,
VDR	Dermatological: Psoriasis Non-dermatological: Insulin resistance, Colon cancer, Depressive symptoms

2. *Neural Hypothesis*

Initially, melanocytes were thought to be regulated by neural mechanisms. Hence, it was thought that degenerative changes in nerves and their endings supplying these melanocytes could be contributing to vitiligo development. [12]

Further, this concept was supported by various neurological disorders being linked with hypo- or de-pigmentation in areas distal to the injury, such as in cases of brachial plexus injury, transverse myelitis and various infective diseases affecting the nerves, spinal cord or brain (tertiary syphilis, leprosy, pinta, and viral encephalitis).[23, 27-29]

Studies have also shown the involvement of the autonomic nervous system to be significant in the pathogenesis of Vitiligo. Increased Catecholamine release can:

1. Cause direct cytotoxic effects on melanocytes
2. Cause oxidative stress by oxidation of Phenol which forms toxic radicals resulting in melanocyte destruction.
3. Result in arteriolar Vasoconstriction, eventually causing skin hypoxia and cell death

3. *Autoimmune Theory*

Vitiligo is, by and large, considered to be an autoimmune de-pigmenting disorder [12]. Strong evidence supporting this theory comes from its frequent association with other autoimmune conditions affecting various organ systems, suggesting a shared underlying immune mechanism.[31, 32]

- *Humoral immunity:* Research indicates that individuals suffering from vitiligo exhibit elevated levels of circulating autoantibodies targeting melanocyte-associated proteins responsible for pigment production as compared to normal individuals [33-37]. Multiple studies using immunoblotting techniques were conducted on vitiligo patients and showed nearly 40-60% of the study population to have autoantibodies against tyrosinase, further supporting the role of humoral immunity.[38, 39]

- *Cell-mediated response:* Biopsies taken from the skin surrounding the active patch of vitiligo consistently showed increased lymphocytic infiltration with a reduced CD4 to CD8 ratio. This led to the hypothesis that cytolytic damage mediated by the active T-cells in the skin of vitiligo patients may contribute to the depletion of melanocytes responsible for the development of vitiligo.[40]

4. *Hypothesis of Oxidative Stress*

Oxidative stress may serve as the primary trigger for damaging melanocytes.[41-44] Increased pro-oxidants and reduced antioxidants in vitiligo have been implicated in making melanocytes more vulnerable to external oxidative stressors.[45-47] This results in a perpetual cycle of oxidative damage. The increased reactive oxygen species can consequently cause free radical-mediated damage to DNA, lipids and proteins, ultimately disrupting melanocyte function and survival.[47, 48]

5. *Auto Cytotoxic Hypothesis*

The aforementioned proteins involved in protein synthesis, specifically TRP-1, can sometimes undergo spontaneous mutations and can result in degeneration of cellular components which can ultimately cause apoptosis of melanocytes. Normally, the process of melanin synthesis within melanosomes is compartmentalized which protects the rest of the melanocyte in case of such mutation. This separation is absent in patients of vitiligo, consequently showing increased programmed death of Melanocytes.[49]

6. *Melanocytorrhagy hypothesis:*

This theory suggests that recurrent trivial trauma can lead to the gradual detachment of melanocytes, contributing to vitiligo progression. This is evident in NSV, where lesions initially appear in areas subjected to repeated physical stress.[12] The altered extracellular matrix synthesis resulting in abnormal structural junctions and structural abnormalities in the dendrites of melanocytes may be responsible for the poor melanocyte adhesion system.[50, 51]

Summary of Vitiligo pathogenesis:[17]

Genetic Susceptibility & Environmental Stress

(Genetic predisposition: polymorphisms in immune-related genes & Environmental triggers:

UV radiation, infections, stress, toxins)

↓

Oxidative Stress & ROS Overproduction

(ROS in melanocytes & decreased antioxidant defenses, e.g., tetrahydrobiopterin imbalance)

↓

Unfolded Protein Response (UPR) Activation

(Cellular stress triggers the UPR & Melanocytes experience endoplasmic reticulum stress)

↓

Melanocyte Exosome Secretion

↓

Dendritic Cell (DC) Maturation & Antigen Presentation

↓

T Cell Activation & Immune dysregulation

(Regulatory T cells [Tregs] become dysfunctional, failing to suppress immune response)

↓

CD8+ T cell Activation & Skin Infiltration

(Cytotoxic CD8+ T cells target melanocytes; Production of IFN-γ)

↓

IFN-γ stimulates the JAK-STAT Pathway

↓

Secretion of chemokine ligand 9 - Recruits CD8+ T cells against melanocytes

Secretion of chemokine ligand 10 –

(enhances the activity of epidermotrophic T cells)

↓

Melanocyte Destruction & Chronic Inflammation

(CD8+ T cells kill melanocytes via perforin/granzyme and Fas-FasL interactions this results in chronic inflammation which creates a positive feedback loop, perpetuating melanocyte loss)

CLINICAL FEATURES

Vitiligo, clinically, is branded with the manifestation of irregular discoloration, appearing as distinct chalky-white or milky patches. to patches. In most cases, the lesions are not associated with itching, scaling, burning sensation, or other local symptoms; however, some patients have experienced itching or burning before or during their onset.[24] Vitiligo can affect any part, but it tends to occur more frequently in areas with naturally higher pigmentation, such as the axilla, face, nipple-areola complex, and genitalia. Additionally, lesions often appear in regions prone to repeated trauma or friction aligning with Koebner's phenomenon.[52]

It is also known as the isomorphic response (from the Greek meaning "equal shape"); this phenomenon occurs when newly formed lesions are clinically and histologically similar to the patient's existing skin condition.[53]

Clinical morphology of Vitiligo may present with varying forms:

1. Trichrome vitiligo: A transitional zone of varying skin pigmentation between a central vitiligo macule and the surrounding normally pigmented skin.[24]
2. Quadri-chrome vitiligo: Four colors in in the same white lesions. This morphological form is more commonly seen in those with Fitzpatrik skin types III to IV and above. Hyperpigmentation around follicles or at the borders of the lesion indicates disease improvement.[54]
3. Penta-chrome vitiligo: Presents with central white pigmentation, with rims of tan, brown and blue to grey pigmentation showing improvement and then the outermost normally pigmented skin.[55]
4. Blue vitiligo: Occurs at the site of post-inflammatory hypermelanosis.[24]
5. Inflammatory vitiligo: Red, elevated, symptomatic macule.[56 -58]

Behl *et al.*[54]introduced clinical staging to aid in management planning :

1. Progressive Vitiligo: It is characterized by the development of new lesions and/or expansion of previously existing ones. The borders are hazy with indistinct demarcation between lesional and normal skin
2. Quiescent Vitiligo: In which there is no appearance of new, and the existing remain stationary. The lesions develop well-defined borders, and some may exhibit hyperpigmented edges, indicating stability in the condition.
3. Improving Vitiligo: it is marked by the decreasing size of lesions, with some areas of depigmentation disappearing over time.

DERMOSCOPY

Dermoscopy, , enhances the visualization of structures that are below the surface level of structures of skin through optical magnification, and cross-polarization of the light.[59]In the last few decades, dermoscopy has proven to be a valuable tool in diagnosing and managing various inflammatory dermatoses, as it reveals critical findings that are not detectable by the naked-eye.[60]

Dermoscopy serves as a valuable tool in vitiligo, allowing for the visualization of subtle characteristics which are not detectable to the bare eyes.[61]In healthy normal skin, pigmentation forms a characteristic reticulate pattern, where darker pigmentation aligns with the rete ridges, while the paler regions match up to the underlying papillary dermis. This intricate pattern plays a fundamental role in maintaining the uniform appearance of skin tone. However, in various pigmentary disorders, including vitiligo, this natural arrangement becomes disrupted.[62, 63]

Dermoscopic features [124]

Feature	Unstable vitiligo	Stable vitiligo
Perifollicular pigmentation	Similarly pigmented compared to normal skin	De- or hyperpigmented compared to normal skin
Pigmentary Network: (Patterns seen: Normal, reduced, absent or inverted)	All patterns except normal Inverted pigment network: depigmented network with intermediate pigmentation.	Reduced or absent pattern: pigment network appearing more white
Intra-lesion	Trichromic pattern: central depigmented area(pseudo-scaring) surrounded by yellow-brown pigmentation and normal skin tone of the patient in the periphery of the lesion	Erythema, telangiectasias (dilated capillaries 1-4mm in diameter) and atrophy (reduced thickness and increasing folding)
Peri-lesional	Comet tail (unidirectional) or Starburst (multidirectional) peripheral extension of depigmentation is seen. Micro-Koebner phenomenon is positive.	Erythema and hyperpigmentation are observed.
Leukotrichia	White hairs present	Less frequently seen in long standing cases

Based on the existing knowledge a scoring system was established in a study by Nirmal B et al.[61] They proposed the acronym 'BPLeFoSK' which represents:

i. **B**order: Sharp (+1), ill-defined/trichrome (0)
ii. **P**igment network: Absent or Reticular (+1), Reduced or Reverse (0)
iii. Peri**le**sional hyperpigmentation when present (+1)
iv. Peri**fo**llicular hyperpigmentation when present (+1)
v. **S**atellite lesion when noted (-1.5)
vi. Micro-**K**oebner phenomenon when noted (-2)

A BPLeFoSK criteria score of 1.5 or higher serves as a threshold for determining the stability of a vitiligo lesion.[61]

DIFFERENTIAL DIAGNOSIS

Numerous dermatoses, some seen more often than others, present with areas of reduced skin pigmentation to complete achromia and should be considered as other likely diagnoses while assessing a case of vitiligo.[17, 24]Occupational vitiligo-like depigmentation occurs commonly due to exposure to phenols and compounds, which are derived from configurational and conformational changes in their chemical structure. Depigmentation can also result secondary to drugs, both topical and systemic drugs, toxic drug reactions, and phototherapy- or radiotherapy-induced effects. Several genetic syndromes are associated with hypo-pigmentation. Piebaldism and Waardenburg syndrome also involve pigmentation defects, often accompanied by immunological or bleeding disorders. Hypomelanosis of Ito is characterized by hypopigmented streaks and whorls that align with the lines of Blaschko , while Tuberous sclerosis manifests with hypomelanotic macules along with other systemic

features. Additionally, Menke's syndrome, a disorder of copper metabolism, and Ziprkowski-Margolis syndrome, a rare inherited condition, can also contribute to pigmentary anomalies. Inflammatory skin conditions, including post-inflammatory hypopigmentation, can lead to temporary or long-lasting pigment loss, while pityriasis alba often presents with faint, scaly, hypopigmented patches that gradually fade over time. Other inflammatory dermatoses, such as atopic dermatitis, allergic contact dermatitis, psoriasis, and lichen planus, can lead to hypopigmented lesions. Hypomelanoses can also be associated with various neoplastic and infective causes. Melanoma-associated leukoderma and mycosis fungoides are examples of hypopigmentary changes linked to neoplasms. Infectious agents responsible for hypomelanosis include mycobacterium leprae, treponema pallidum, parasitic infection like leishmaniasis . Also it is seen in pinta, pityriasis versicolor and Onchocerciasis,. Some cases arise without a known cause, as seen in idiopathic guttate hypomelanosis, progressive macular hypomelanosis and acquired macular hypomelanosis. Certain congenital conditions, including nevus anemicus and nevus depigmentosus, are characterized by localized hypopigmented skin patches present from birth.[17, 64-68]

TREATMENT OPTIONS

Topical

Corticosteroids: Steroids, even till date, remain the main stray for treatment of vitiligo. The immunomodulatory and anti-inflammatory properties of corticosteroids are made use of in treating vitiligo patients.[69, 70, 71] The recommended regimen for topical corticosteroids (TCs) is daily application for up to 3 months, followed by intermittent application for a maximum of

6 months. TCs need to be discontinued if no improvement even after 3-4 months of usage.[69, 72, 73] The side effects include local changes like thinning of skin with visible dilated blood vessels, striae, increased hair-growth, and acne-like eruptions, and systemic effects like adrenal suppression.[74]

Calcineurin inhibitors: Tacrolimus (0.03% or 0.1%) and Pimecrolimus (1%), are used for vitiligo treatment, particularly for areas on the head and neck.[75] The functioning of the drug can be explained as follows:[76]

Calcineurin Inhibitors (e.g., Tacrolimus, Pimecrolimus)

↓

Inhibition of Calcineurin

↓

Prevention of IL-2 & TNF-α Transcription

↓

Reduced IL-2 and TNF-α → Reduced T-cell activation and decreased inflammation

↓

Reduced Cytokine Formation

↓

Induction of Melanocyte &Melanoblast Proliferation

↓

Enhancement of Repigmentation in Vitiligo

Controlled daily sun exposure is recommended as part of the treatment. Topical calcineurin inhibitors (TCI) may be administered either as standalone therapy or in combination with other treatments. Common complaints of the patients after TCI usage include a feeling of itch or burn. They also result in an increased risk of acquiring skin infection, more commonly viral infection.[75]

Vitamin D3 analogues: Topical vitamin D3 analogues exert their immunomodulatory effect by inhibiting T-cell activity, aiding the development of both melanocytes and melanosomes.[74, 76] They are ineffective as standalone but are good addition to other modalities of managements used for vitiligo. It is ideally used along with TCs like topical calcipotriol 0.005% or betamethasone 0.05%. These topical agents are safe in both children and adults, and only reported side effect is mild irritation.[75]

Pseudocatalase/superoxide dismutase: The current data doesn't support its usage as being beneficial as compared to NBUVB. Its proposed mechanism is based on its ability to reduce the melanotoxic effect and tyrosinase inhibitory effect exerted by reactive oxygen species.[77] However, there is insufficient information available on the safety profile and potential adverse effects.[78]

5-Fluorouracil (5-FU): 5-FU spurs on the follicular melanocytes and assists their migration subsequently increasing the number of melanosomes in the epidermis.[79, 80] These drugs too, though, are not free of side effects. They are known to damage the skin causing ulceration and scaring. They also increase the risk of local infection and delay wound healing.[78, 81]

Methotrexate (MTX): Folate is essential for T cells which mediate the autoimmunity of vitiligo. MTX is a folate antagonist, and studies have suggested that it has anti-inflammatory and immunomodulatory effect. Significant improvement in the pigmentation has been observed with MTX 1% gel. However, the safety profile and efficacy are still a question of much debate.[82]

Basic fibroblast growth factor derived peptide: These growth factors aid migration of melanocytes but is not free of deleterious effect including skin irritation, dryness, and burning.[75, 83]

Systemic treatment options

Corticosteroids: It suppresses the immunity and turns unstable form to a stable one. Patients receiving steroids as a treatment are at risk of menstrual irregularities, metabolic disturbances, and infections and need to be routinely monitored for the same.[75] Other minor adverse events include fatigue, insomnia, and cutaneous effects similar to TCs.[84, 85, 86]

Apremilast: Phosphodiesterases (PDE) are a group of enzymes which metabolize intracellular cyclic adenosine monophosphate (cAMP), which is required to control inflammation Apremilast is a PDE-4 inhibitor, thus increases cAMP and consequently exerts an anti-inflammatory effect.[87] The drug is known to cause mild side effects like nausea-vomiting, pain abdomen and headache.[87, 88]

Minocycline: Minocycline, prescribed at a dose of 100mg once daily, has been shown to have anti-oxidative effect and is especially beneficial in early stages of the disease.[89] It can cause - nausea, vomiting, gastritis and pain abdomen. and also Muco-cutaneous effects in the form of hyperpigmentation are also seen.[90, 91]

Statins: , It has an anti-inflammatory and immunomodulatory effects.[92-95] They also have a role in reducing the oxidative stress.[92]Although, Statins have been hypothesized to theoretically help in vitiligo, but studies have failed to translate these theories into any tangible practical benefits.[74]

MTX: The mechanism as already discussed is via inhibition of folate synthesis. The systemic drug is recommended to be taken only once a week at a dose of 7.5-25.0 mg. It is recommended to add, .with folic acid supplementation along-side the weekly antimetabolite dose to counter side effects like hepatotoxicity and pancytopenia. It is usually initiated with a test of 5-7.5mg/week to look for idiosyncratic pulmonary toxicity which is sometimes observed post intake of MTX. Other minor side effects include nausea, vomiting, and diarrhea.[74]

Azathioprine: Azathioprine inhibits DNA synthesis in rapidly replicating cells like leukocytes thus, while helpful in treating immune-mediated conditions like vitiligo, they can result in severe side-effects of myelosuppression and heightened risk of infections. Other adverse events associated include liver toxicity, gastric symptoms, and hypersensitivity reactions .[74]

Cyclosporine: Its action is similar to topical agents acting on the later molecule. Although, studies have shown it to be significantly helpful in treating Vitiligo, it is also associated with tragic side-effects affecting multiple organ systems like renal, musculoskeletal and cardiovascular system. It is also known to cause electrolyte imbalances like increased serum calcium and urea, and in the muco-cutaneous system it causes hypertrichosis and gum hypertrophy.[74, 96]

Physical therapy

Phototherapy is a well-established treatment for vitiligo, utilizing ultra-violet wavelengths of light to modulate the immune response and thus stimulate repigmentation. Among the available options, NBUVB phototherapy, which emits light at 311 nm, and is preferred over broad-spectrum modalities, due to its effectiveness in suppressing autoimmunity, promoting melanocyte migration, and enhancing melanin synthesis.[97]

PUVA therapy, a second-line treatment, involves the administration of psoralen—a photosensitizing agent—either orally or topically, followed by UVA exposure (320-340 nm). PUVA promotes melanin production, though its use is typically reserved for cases where other therapies have proven inadequate.[74, 97]

Excimer

The term "excimer" is derived from "excited dimer," referring to a molecular complex that dissociates when it returns to the ground state. These species play a crucial role in various applications, including laser technology, phototherapy, and fluorescence spectroscopy.

Principle: When an excited-state molecule interacts with a ground-state counterpart it leads to

a bound excited-state complex. This forms the energy of the Excimer which is lower than the sum of the individual molecular excitations. Upon returning to the ground state, the complex dissociates due to the lack of a binding force in this state. Common Excimer-forming molecules include noble gas-halogen combinations (e.g., XeCl, KrF) and certain organic aromatic molecules.[60]

Surgical options

Surgical methods are advised in stable form of the disease which are non-responsive to medical modalities of treatment.[17] These include:[9, 13, 17]

- Grafts from normal tissues: which could be harvested as full-thickness grafts which, include dermis as well using a punch, or split-thickness which excludes the dermis, and suction blister grafts were negative pressure is used to from blisters separating dermis from epidermis and the later is then harvested
- Grafts using only cellular components i.e. the melanocyte which could be either cultured or non-cultured
- Cultured epidermal suspensions and hair follicle transplantation

However, each of these treatments has proven to not be reliably effective. A newer upcoming area of research is biological therapies for Vitiligo.[1, 3] JAK inhibitors synthetic molecules that interrupt the JAK-STAT signaling pathways, leading to the inhibition of multiple immune-mediated inflammatory pathways.[98] Recently, these have come up as miracle drugs for the treatment of adults with vitiligo.[1, 2–4]

JAK Inhibitors and Vitiligo

History

Early studies in animal models found that blocking interferon gamma antibodies lead to loss of pigmentation in lesions. JAK inhibitors effectively inhibit IFN-γ signaling and, thus, aid in the restoration of pigmentation in individuals with vitiligo.[1]

Pathophysiology of JAK-STAT Pathway

Activation of JAK receptors triggers the phosphorylation of STAT transcription factors. JAK are cytosolic surface receptors while STATs are present in the cytoplasm. Once phosphorylated, they enter the nucleus and influence the transcription of genes involved in inflammation. The JAK-STAT pathway is a complex signaling cascade where the 1st step is set forth by binding of a cytokines which act as ligand to the receptors various JAK receptors (JAK1, JAK2, JAK3, and tyrosine Kinase 2 enzymes).[99, 100, 101]

In vitiligo, as discussed previously, INF-γ interacts with CXCL10 resulting in melanocyte apoptosis.[17,103] INF-γ acts as a ligand for JAK1/2 receptors and there-in mediates its action; therefore, the use of the JAK1/3 inhibitors like Tofacitinib will help in protecting the melanocytes from apoptosis and exert their therapeutic effect.[4]

Classification

There are two generations of JAK inhibitors. Small compounds like baricitinib and tofacitinib, which function as non-selective inhibitors of JAKs, are part of the first generation. Filgotinib and upadacitinib are examples of second-generation medications that selectively inhibit JAKs.[104]

Additionally, JAK inhibitors can be categorized according to how they bind and interact with the amino acids, such as reversible and irreversible types. Reversible JAK inhibitors are of two types. Drugs such as Filgotinib, Fedratinib, Tofacitinib, and Peficitinib are type one which bind and competitively inhibit the binding of ligand, and drugs such as NVP-BBT594 and NVP-CHZ868 are second type which non-competitively inhibit the receptor.[27,34] Irreversible JAK inhibitors are Ritlecitinib, Deucravacitinib and LS104. [105,106]

Indications in Dermatology

Tofacitinib, was initially meant for renal transplantation. Tofacitinib has since long attained FDA approval for rheumatic diseases, initially indicated for rheumatoid arthritis (RA) in patients with an inadequate response to conventional synthetic DMARDs (csDMARDs).[108,109]Its approved indications have since expanded to include psoriatic arthritis [110,111] and ulcerative colitis.[112]

Others approved in DMARD incomplete responder cases of RA include Baricitinib (a JAK1/JAK2 inhibitor), Peficitinib (pan JAK inhibitor), Upadacitinib (JAK1 selectivity), and Filgotinib (JAK1 selectivity) which have been variably approved in different regions of the world.[108,113-116]

Baricitinib has also been given an approved status in atopic dermatitis in Europe. Ongoing research is exploring additional indications for Tofacitinib, including serious systemic disorders like systemic lupus erythematosus, relapsing giant cell arteritis, and myasthenia gravis alongside mentally taxing dermatological disorders like alopecia areata and Vitiligo.[108]

Studies have documented JAK inhibitors in cases of vitiligo, including 5 mg once a day. In Vitiligo, re-pigmentation has been documented with the use of Tofacitinib and

Ruxolitinib.[102,107]

Tofacitinib in Vitiligo

Topical and oral forms of Tofacitinib have shown promising results in treating disorders such as vitiligo, plaque psoriasis, alopecia areata and atopic dermatitis.[1, 3, 108]Interferon γ signaling induces melanocyte at least destruction by CD8 T cells. Tofacitinib inhibits this mechanism.[117] In some studies, it was mentioned that 5 to 10 mg of Tofacitinib per day can cause satisfactory re-pigmentation.[26] In other studies, it was mentioned that better outcomes were observed in sun-exposed areas or with concomitant administration of phototherapy .[1, 3, 117]

Special Considerations of Tofacitinib

Tofacitinib has specific safety considerations across different populations. As a pregnancy category C drug, its use during pregnancy should be approached with caution. Its secretion occurs in the breast milk of lactating females, and breastfeeding should be avoided during treatment. Breastfeeding should be avoided at least 18 hours after the last dose. In extended-release formulation, breastfeeding should be avoided at least 36 hours after the last dose The safety of Tofacitinib in individuals below 18 years has not established, making its use in pediatric population uncertain. In the geriatric population, infectious events are reported commonly in elderly patients receiving Tofacitinib orally, necessitating careful monitoring in this age group.[117,118,119]

Adverse effects

Various research related to safety and tolerability of JAK inhibitors is ongoing.[1, 2, 120]Some of the commonly observed adverse events

Infections: Individuals who are on JAK inhibitors are prone to various bacterial, fungal and viral infections. Hence, these individuals should be followed up constantly for latent infections, and screening for infection must be done.[120]

Hematological Effects: Hematopoiesis can also be affected by JAK inhibitors, which may cause changes in blood cell count and may cause anemia, lymphopenia and neutropenia. These hematological changes may occur due to the inhibition of JAK2, a kinase which are necessary for the production of blood cells. Hence, regular evaluation of hematological parameters such as complete blood cell count is necessary.[120, 121]

Cardiovascular Risks and Thrombosis: In some research studies increased incidence of cardiovascular and thrombo-embolic events was noted. These changes are especially associated with higher doses. Hence, it is essential to check the patient for associated cardiovascular risk factors before starting the treatment. Also, regular follow-up for symptoms of cardiovascular diseases and thrombosis is important.[120]

Malignancies: Usage of Tofacitinib is associated with malignant tumors of the skin and lymphoma cutaneous carcinomas. Association of solid organ malignancies was also reported.[117]

Gastrointestinal: In some studies, gastrointestinal perforations and obstruction are also reported.[117,118]

Hypersensitivity reactions and miscellaneous: Various hypersensitivity reactions such as

angioedema and urticaria can occur due to Tofacitinib therapy. Other adverse effects, such as hypertension and headache, are also reported. Association of JAK inhibitors with musculoskeletal complaints such as arthralgia, pain in extremities, back pain, and distal symmetric polyneuropathy is also reported.[117,122]

General monitoring guidelines

- Baseline screening investigations for monitoring patients on JAK inhibitors are complete blood cell count and various biochemical tests such as liver function tests (LFT), serum creatinine, serum creatinine phosphokinase levels, fasting lipid profile and tests for hepatitis B and C virus, and test for HIV.[1, 4]
- Screening for tuberculosis, such as the Mantoux test or Gold Quantiferon test, must be done with Interferon-γ release assay.[107]
- Patients receiving Tofacitinib require regular monitoring to ensure safety and detect potential adverse effects. After 1 month of treatment and then every 3 months, laboratory tests, including hematological profile, serum creatinine, liver enzyme, and fasting lipid profile, should be performed. Annual screening for tuberculosis is recommended to monitor for latent or active infection. Additionally, diagnostic evaluations should be conducted as needed if an infection is developed or reactivated during the course of or after completion of treatment.[117,119,123]
- In patients with moderate to severe hepatic impairment and renal insufficiency dosage adjustment to half the daily dose is needed.[117]

Contraindications:

Tofacitinib has both absolute and relative contraindications that must be considered before initiating treatment:[117, 119, 122]

Category	Conditions
Absolute Contraindications	Active infections, including tuberculosis, opportunistic infections, cellulitis, and sepsis, as well as viral infections.
	Severe decrease in hematological parameters such as Hemoglobin, lymphocytes and neutrophils
	Severe impairment of liver function.
	Hypersensitivity to Tofacitinib or its components.
Relative Contraindications	History of chronic or recurrent infections or previous serious or opportunistic infections.
	Previous exposure to TB or a history of hepatitis B.
	Presence of interstitial lung disease or any lung disease
	Increased risk of gastrointestinal perforation or severe pre-existing gastrointestinal narrowing.
	History of malignancy.

Oral v/s Topical Tofacitinib

Topical formulations of JAK inhibitors help mitigate the adverse effects associated with their oral counterparts. Topical Tofacitinib, commonly used as a 2% ointment, can be applied with or without penetration enhancers. It has shown modest improvement in psoriasis and atopic dermatitis, though its efficacy is lower than oral Tofacitinib and comparable to clobetasol 0.05% ointment under occlusion.[118, 125, 126]

In vitiligo, topical Tofacitinib cream has demonstrated more significant responses, especially in patients with darker skin tones and facial lesions.[1, 6] The commonly reported adverse effects include hyperpigmentation, erythema, and transient acne, along with minor, reversible laboratory abnormalities.[6, 118] The use of topical Tofacitinib reduces systemic exposure, thereby avoiding many of the systemic side effects seen with oral Tofacitinib.[1, 118]

At present, there are limited registered clinical trials evaluating topical Tofacitinib for vitiligo treatment, highlighting the need for further research to assess its efficacy, safety, and potential role in combination with phototherapy.[1, 6, 118]

MATERIALS AND METHODS

1. **SOURCE OF DATA: V**itiligo patients coming to Dermatology OPD
2. **STUDY DESIGN:** An open label, non-randomized, interventional study
3. **STUDY PERIOD:** 1 year
4. **SAMPLE SIZE:** Calculation of sample size was done by using G-POWER under F tests for ANOVA : Repeated measures , within factors considering effect size to be 0.25, alpha=0.05, beta = 0.10, power of the test = 0.90, number of groups = 2, number of measurements = 4 , correlation among repeated measures = 0.5 , non-sphericity correction = 1 , we got sample size as 30. We took 30 patients and 2 similar patches anywhere on the body from each patient and used for the study.
5. **SAMPLING TECHNIQUE:** Purposive sampling
6. **INCLUSION CRITERIA AND EXCLUSION CRITERIA**
   a. Inclusion criteria: Patients of vitiligo aged 15 to 65 years, with ≥ 2 depigmented patches, both ≤10% BSA, who were willing to consent.
   b. Exclusion Criteria: Study participants with only acral lesions, pregnant women (safety profile unknown) and patients refusing to be a part of the study were excluded.
7. **STUDY PROTOCOL:**

Sample size (n=30)

↓

Informed consent was be taken

↓

Baseline data was collected

↓

2 similar patches were selected at random & treated with topical tofacitinib 2% twice daily

↓

1 of the selected patches was treated with targeted UVB at a frequency of twice per week

↓

Patients were followed up for 12 weeks

↓

Assessment using appropirate parameters was done at baseline, 4th, 8th and 12th week

8. **METHOD OF COLLECTION OF DATA:** All the patients falling under the inclusion coming to KLEH's DVL OPD were enrolled in the study.

a. History and Examination

b. Base line investigations: complete blood count, liver function test and renal function test

c. Wash out of treatment: for patients already on treatment for the condition:[2]

i. Topical treatment for 2 weeks

ii. Immunomodulating oral medications for 4 weeks

iii. Phototherapy/excimer for 8 weeks

d. **Intervention done:** 2 depigmented patches were selected and given topical Tofacitinib 2% cream application twice daily. 1 of the 2 patches was treated with targeted UVB.

e. **Targeted UVB therapy:** Administered via an Excimer laser of 308nm for 10 seconds at 200mJ with an increment of 10% per week.[5]

f. Assessment of treatment outcome:

i. **Vitiligo area scoring index (VASI): VASI score calculation was done as per the study done by Joshipura D et al.[2] by** multiplying affected BSA

(which were estimated by use of hand units) by the degree of depigmentation (0-100%) within each hand unit (possible range, 0-100).[2]

ii. **Photographs:** Clinical images of vitiligo patches were taken after every 4 weeks to monitor progression of the condition

iii. **Dermoscopic assessment:** Dermoscopic evaluation of the lesion was done at baseline and again at the end of the study/at 12 weeks. Key features recorded included perifollicular pigmentation, leukotrichia, pigment network, intralesional hyperpigmentation, erythema, and telangiectasia.[124]

RESULTS AND OBSERVATIONS

With the objective to understand the efficacy of topical Tofacitinib and to compare its efficacy in patients of vitiligo, 34 study participants (17 Females and 17 males) were included in the study. Mean age of study participants was 32.32±14.46. A majority (11) of the participants were in the age range of 21-30 years, followed by 11-20 and 41-50 years, with 7 participants in each group.

Table 1: Age and Sex Details of Study Participants

Parameters	Details of age and sex	Total number of cases (n=34)	Percentage (%)
Sex	Male	17	50
	Female	17	50
Age	11 -20	07	20.59
	21-30	11	32.35
	31-40	04	11.76
	41-50	07	20.59
	51-60	04	11.76
	61-70	01	2.94

The clinical variables noted included the Fitzpatrick skin scale, of which most of the participants had either type III (10) or IV (10). The mean duration of the disease noted was 67.82±81.04 months. Prior history of trauma was noted in 6 study participants. In 4 patients family history of vitiligo was present . The patches included in our study were predominantly present over sun-exposed areas, maximum, i.e., 6 cases showed involvement of face, and other sites involved were elbows, feet, abdomen, legs, fingers, knee, chest, forearm and hands.

Table 2: Details of Clinical Variables in Study Participants

Characteristics		N=34	%
Fitzpatrick skin type (I-VI)	I	00	00
	II	01	2.94
	III	10	29.41
	IV	10	29.41
	V	13	38.24
	VI	00	00
Duration of disease – months	Less than 6 months	05	14.71
	7 -12	07	20.59
	13 – 36	04	11.76
	37-60	06	17.65
	More than 60 months	10	29.41
Location of the patch	Face	06	17.65
	Chest	02	5.88
	Abdomen	03	8.82
	Arm	02	5.88
	Fingers	02	5.88
	Legs	11	32.35
	Elbows	05	14.71
	Knees	03	8.82
History of trauma prior to onset	Present	06	17.65
	Absent	28	82.35
Family history	Yes	04	11.76
	No	30	88.24

The baseline VASI in JAK+Excimer group was 0.189±0.28 and in JAK only group was 0.172+0.25. The difference between the 2 was not statistically significant (p=0.768). The VASI at 4th week in JAK+Excimer group was 0.161±0.24 and in JAK only group was 0.163±0.25. The difference between the 2 was not statistically significant (p=0.99). The VASI at 8th week in JAK+Excimer group was 0.109±0.17 and in JAK only group was 0.128+0.19. The difference between the 2 was not statistically significant (p=0.731). The baseline VASI in JAK+Excimer group was 0.043±0.06 and in JAK only group was 0.059+0.08. However, the difference between two groups was statistically not significant (p=0.477).

Table 3: Comparison of improvement in VASI in both groups

	JAK+ Excimer		JAK only		p-value
	Mean	Stander Deviation (SD)	Mean	Standard. Deviation(SD)	
Baseline	0.189	0.275	0.172	0.253	0.768
4th week	0.160926	0.2396565	0.162868	0.2515199	0.990
8th week	0.109324	0.1654889	0.128147	0.1943848	0.731
12th week	0.04324	0.06111	0.0593	0.07882	0.477

The VASI amongst both the groups improved significantly at the end of 12 weeks. Statistically significant improvement in VASI was noted in JAK+Excimer group at all intervals; at end of week 4 the difference was 0.868 (p=0.06), from week 4 to week 8 it was 1.059 (p=0.001) and week 8 to 12 it was 0.926 (p=0.019). [Table 4]

Table 4: Improvement in VASI at each follow up in JAK+ Excimer group

	Mean	p-value
Baseline vs 4th week	0.868	0.006*
4th week vs 8th week	1.059	0001*
8th week vs12th week	0.926	0.019*
*p-value (< 0.05) statistically significant		

We also observed statistically significant improvement in VASI in JAK only group but only at 4thweek and at 8th week; at end of week 4 the difference was 0.500 (p=0.11), from week 4 to week 8 it was 1.162 (p=0.001) and week 8 to 12 it was 0.941 (p=0.016). [Table 5]

Table 5- Improvement in VASI at each follow up in JAK only group

	Mean	Std. Deviation
Baseline vs 4th week	0.500	0.110
4th week vs 8th week	1.162	0.001*
8th week vs12th week	0.941	0.016*
*p-value (< 0.05) statistically significant		

The improvement in VASI was more in JAK+Excimer group as compared to JAK only group. The difference between the 2 groups from baseline was statistically significant at all intervals. The improvement was statistically higher in JAK+Excimer arm compared JAK only group. [Table-6]

Table 6- Overall Difference in VASI between the 2 groups from baseline

	JAK+ Excimer		JAK only		Significant value
	Mean	Std. Deviation	Mean	Std. Deviation	
4th Week	0.160926	0.2396565	0.162868	0.2515199	P=0.990
8th Week	0.4552	0.18123	0.3195	0.24777	P=0.001*
12th Week	0.7407	0.18009	0.6208	0.25337	P=0.013*
*p-value (< 0.05) statistically significant					

Images of vitiligo patches before and after treatment:

There was noticeable re-pigmentation observed on serial photography in both the arms in cases which corresponded with the improving VASI of those cases. [Figures 1 and 2]

Dermoscopic Images

On dermoscopy we observed improvements in terms of perilesional/perifollicular pigmentation, reversal of pigment network and the improvement corresponded with the digital photographic improvement seen in respective cases. [Fig 3 & 4]

Safety profile

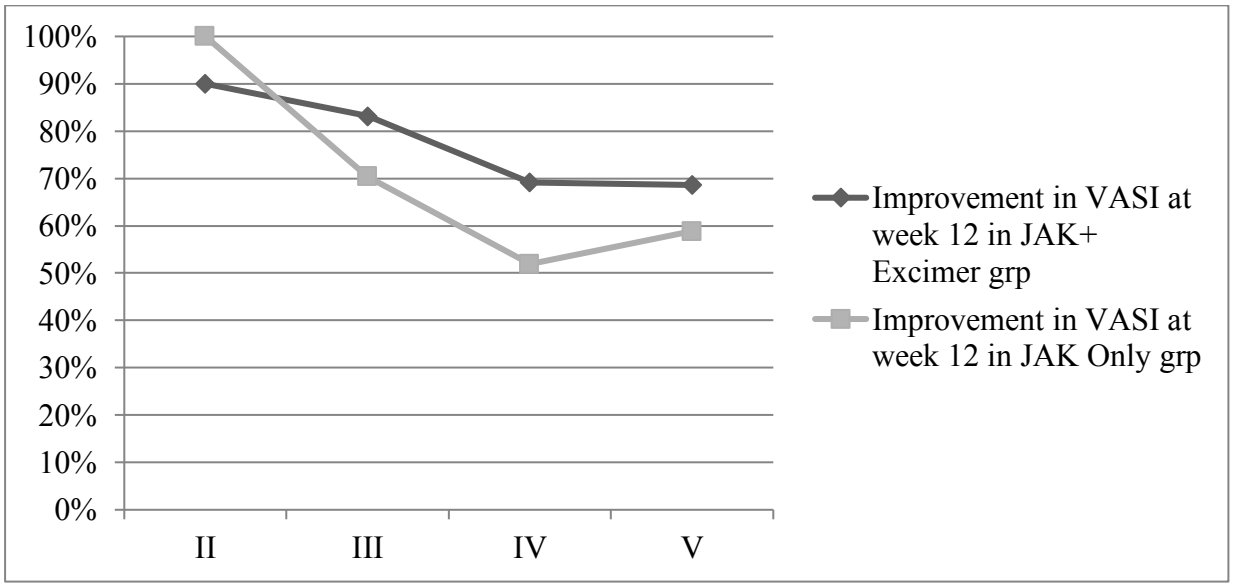
The side effects were noticed only in JAK+Excimer group which included Erythema in s6 cases (Figure 5), Post inflammatory hyperpigmentation in 2 cases (Figure 6), burning sensation in 1 case and desquamation in 1 case (Figure 7). But all of these were transient and subsided within 1 -2 weeks. In patients who developed erythema or burning sensation after Excimer laser the dose was reduced at every subsequent setting.

Variation with clinical variables:

The clinical variables such as Fitzpatrick skin type, location of the patch, duration of disease, history of trauma prior to onset and family history also showed to affect the improvement in VASI.

There was declining trend in response to treatment in both groups with increasing Fitzpatrick skin scale. Better improvement was seen in JAK+Excimer group in all skin types included in the study, except in Fitzpatrick skin type II, where we observed better improvement in patches treated with topical JAK inhibitor only. [Figure 8]

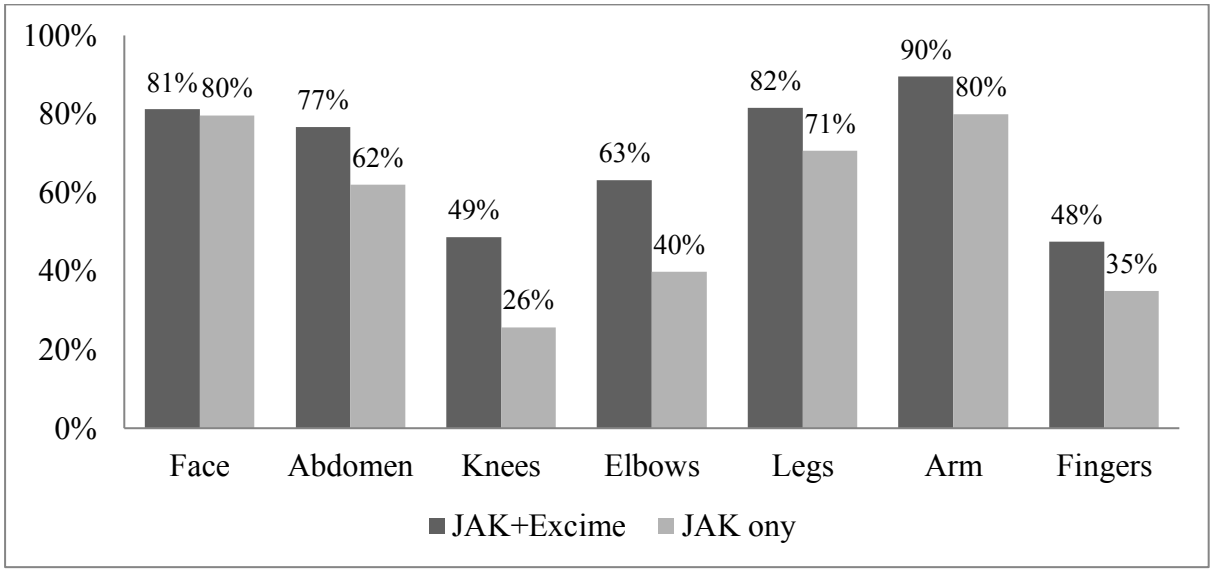
Chart 1: Improvement in different Fitzpatrick skin types



Based on the location of the lesion, more percentage improvement in VASI, in both JAK+Excimer group and JAK only group, was seen in sun exposed areas like arm (JAK+Excimer-89.50%; JAK only-80.00%; Mean-84.75%) and face (JAK+Excimer-81.17%; JAK only-79.67%; Mean- 80.42%). Least improvement was seen in lesions present over acral areas like fingers (JAK+Excimer-47.50%; JAK only-35.00%; Mean-41.25%) and over bony prominences like elbows (JAK+Excimer-63.20%; JAK only-39.80%; Mean-51.50%) and

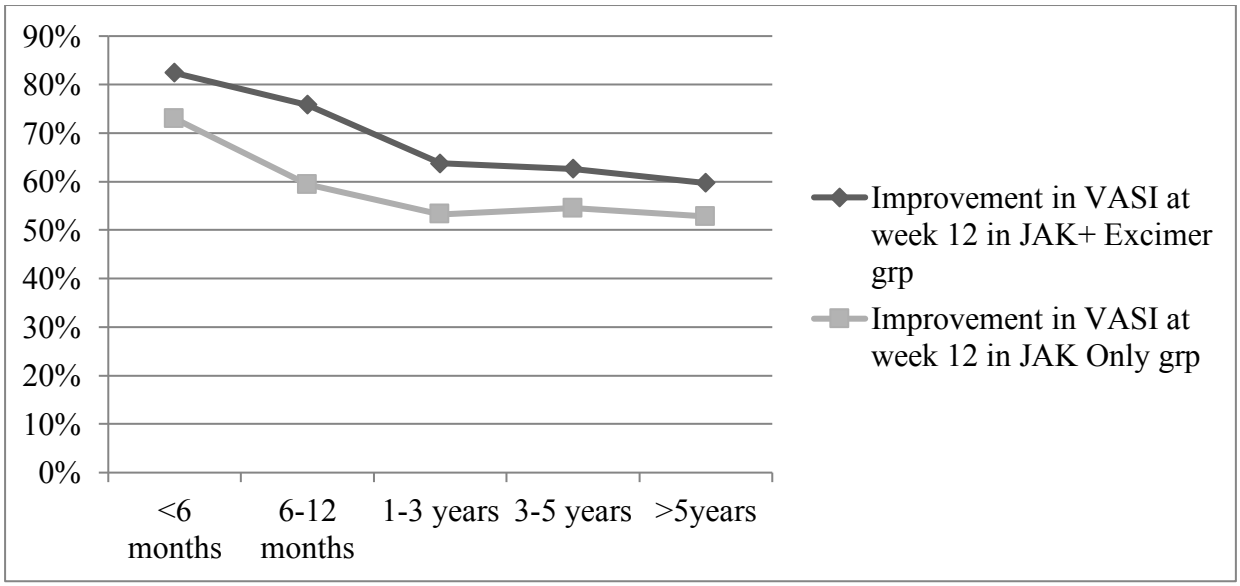
knees (JAK+Excimer-48.67%; JAK only-25.73%; Mean-37.20%). [Figure 9]

Chart 2: Percentage improvement in VASI at week 12 in different anatomical sites



On plotting the improvement in VASI against the duration of the disease, we observed that the lesser the duration the better the response to treatment was. There was a reduction in response as the duration of the disease increased and, in all age, ranges better improvement was observed in JAK+Excimer group. [Figure 10]

Chart 3: Improvement in VASI at week 12 and in different age ranges

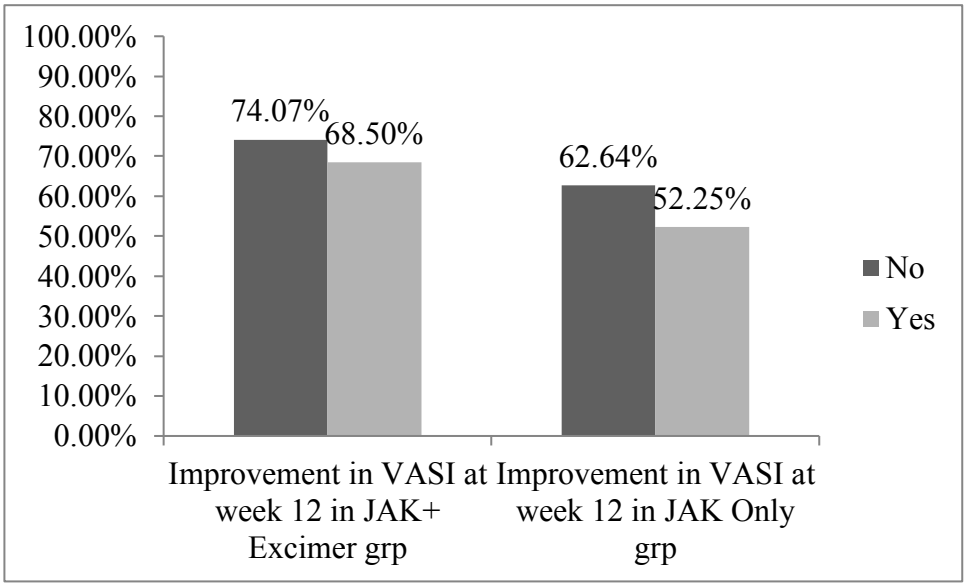


We noted that the improvement in VASI was higher in those who had no family history of the disease when compared to those who did. We found difference in VASI between two study groups was statistically significant only in those who had no family history of the disease (JAK+Excimer: mean dif-0. 7407; JAK only- 0.6264; p-value- 0.022). We observed that there was lesser improvement in VASI at week 12 in those who had a family history of vitiligo, but the association was not found to be significant in either of the group (JAK+Excimer: r=−0.10, p=0.57; JAK Only: r=−0.14, p=0.45) indicating only a week negative co-relation between presence of family history and improvement in VASI. [Figure 11]

Table 7: Family History affecting improvement in VASI between the 2 groups

	JAK+ Excimer 12th week		JAK 12th week		Significant value
	Mean	Std. Deviation	Mean	Std. Deviation	
Yes	0.685	0.16906	0.5225	0.24545	0.248
No	0.7407	0.18425	0.6264	0.25793	0.022*
*: Statistically significant					

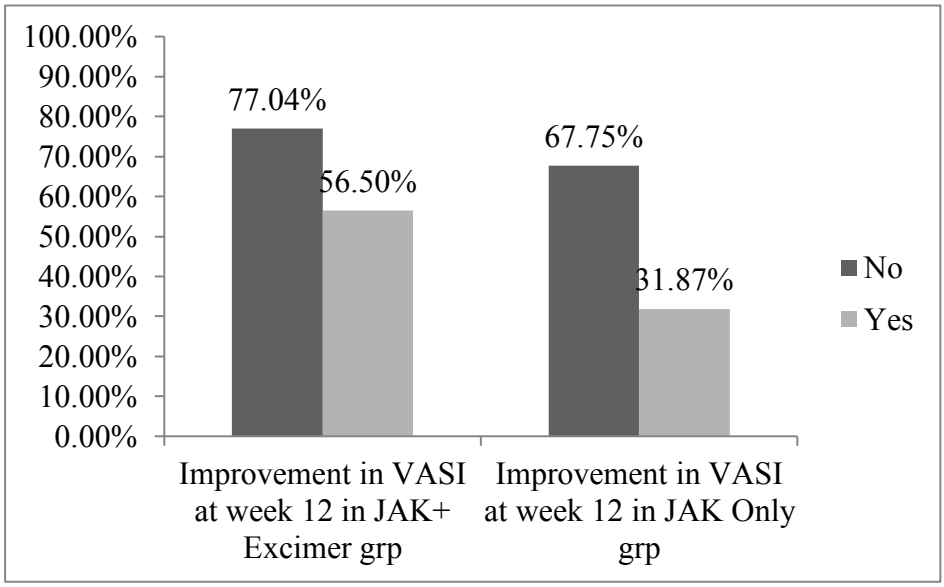
Chart 4: Co-relation between improvement in VASI at week 12 and Family history of Vitiligo



JAK+Excimer: r=−0.10, p=0.57; JAK Only: r=−0.14, p=0.45. r-value showing negative co-relation between VASI improvement and presence of family history. p-value >0.05 not statistically significant.

We observed that in both the groups there was lesser improvement in VASI at week 12 in those who had prior history of trauma. In both groups the association was found to be statistically significant (JAK+Excimer: r=−0.44, p=0.009; JAK Only: r=−0.55, p=0.0007) indicating moderate and strong negative correlation between presence of family history and improvement in VASI in JAK+Excimer and JAK only group respectively. [Figure 12]

Chart 5: Co-relation between improvement in VASI at week 12 and History of trauma prior to onset of the disease



JAK+Excimer: r=−0.44, p=0.009*; JAK Only: r=−0.55, p=0.0007*. r-value showing negative co-relation between VASI improvement and presence of history of trauma. *p-value <0.05 statistically significant.

DISCUSSION

Vitiligo is an age-old disease dating back to 1500 BC and is still a prevalent chronic disease affecting all ages indiscriminately.[8 ,9, 10] Multiple treatment modalities were tried for the treatment of vitiligo. [11] Corticosteroids, both topical and systemic, have been the main stray of treatment for both stable and unstable forms of the disease, but the usage of these is not without side-effects and even so the response observed is not satisfactory.[12, 13, 14] Multiple other modalities have been tried but all of these have been tried with only limited success.[11,14]

Phototherapy was one of the established mode of treatment. ,[15]but as a stand- alone it is associated with multiple side-effects like purities, burns of varying degrees, dryness and few serious adverse effects like malignancies.[14]

JAK inhibitors, like Tofacitinib, have been recently introduced for treatment of multiple auto-immune conditions.[17,18,19] It has been, off-label, used in Vitiligo and shown to be effective in all variants of Vitiligo, with variable out-comes.[1, 3, 20] Systemic usage of the drug can lead to increased risk of infections, thromboembolism, malignancies and hematological derangements like anemia, neutropenia and lymphopenia.[21,22]These can be avoided by usage of topical creams.

Assessment of Efficacy of Administered Treatment

In our study we observed a linear decline in VASI at each 4-weekly interval, but the difference between the mean VASI of both groups was noted to be not statistically significant at any of the study intervals (p-value at 4th week-0.990; p-value at 8th week-0.731; p-value at 12th week-0.477). This improvement also reflected in the serial photographs taken. The average improvement in VASI of 74.07% in group where topical 2% Tofacitinib was used concurrently with Excimer and 62.08% in group of participants using topical Tofacitinib only.

In a study by M K Jacqueline et al.[7], where they tried 2% topical Tofacitinib cream used two times a day along with NB-UVB administered thrice a week for 2-4 moths in 11 vitiligo patients with facial lesions who had failed to respond to previously tried topical treatments they observed a mean VASI improvement of 70% which was similar to what we observed in indexed study. Study conducted by Mobster P et al.[6] observed an improvement of ≥ 90% in 4, 25-75% in 5 and only 5–15% in 4 patients.

In the indexed study, the difference in the mean improvement from baseline between the two groups showed a more favorable result in the group where Excimer was used adjunctively at all study intervals and was statistically significant at both week 8 and week 12 (p=0.001 and p=0.013 respectively) with a higher statistically significant improvement being noted in the week 8 as compared to week 4 and week 12. The mean improvement in VASI between each consecutive 4 weekly interval also showed statistically significant improvement, except from baseline to 4th week in Topical JAK only group. The maximum mean improvement in both groups was observed from week 4 to week 8 (JAK+Excimer: Mean difference- 1.059, p value-0.0001; JAK+Excimer: Mean difference- 1.162, p value-0.001).

These findings suggest that Excimer laser therapy significantly enhances the therapeutic response in vitiligo, particularly in the mid-phase of treatment, which is consistent with the findings mentioned in prior studies demonstrating its efficacy in stimulating melanocyte activity and proliferation.[126, 127] Similar to our study, Gao et al.[1] conducted a pilot study and they observed that the addition of 308-nm excimer laser therapy significantly accelerated and improved repigmentation compared to Tofacitinib alone. McKesey and Pandya et al.[7]investigated the combination of 2% tofacitinib cream with NB-UVB for facial vitiligo, showing enhanced repigmentation outcomes compared to monotherapy. The laser's targeted stimulation of melanocytes, coupled with the immunomodulatory effects of tofacitinib, is hypothesized to create a synergistic therapeutic effect.[1,7,126]

Dermoscopic Evaluation

Dermoscopy provided valuable insights into the repigmentation process. Improvements in peri-lesional and peri-follicular pigmentation, as well as reversal of the pigment network, were more pronounced in the JAK+Excimer group. This aligns with Wang et al.[60], who observed perifollicular hyperpigmentation and a re-established pigment network in patients undergoing 308-nm excimer laser therapy. The study by Errichetti et al.[61] also supports this observation, identifying peri-follicular pigmentation as a reliable interpreter of treatment response in vitiligo patients receiving NB-UVB therapy, reinforcing the role of phototherapy in melanocyte activation. This indicates the role of phototherapy as an important mode of treatment as in stimulating melanocyte activity, eventually, leading to enhanced repigmentation. In previous studies where Excimer laser therapy was done, similar observations were noted. .[128, 129]

Safety Profile and Adverse Events

We observed only mild and transient side effects associated only in the patches exposed to Excimer concurrently with topical tofacitinib, while usage only of topical Tofacitinib showed no associated adverse effects. A case series by Joshipura D et al.[2] where topical Tofacitinib was tried in 6 pts of vitiligo and observed minimal and reversible side effects including minimal acne flair and erythema. We noted mild transient erythema in 6 cases, burning sensation and desquamation in one case, all of which were noted either after the 1st or second sitting of Excimer following which the targeted NBUVB was re-initiated at a lower dose and gradually up-dosed thereafter and the complaints subsided. Post inflammatory hyperpigmentation was another bothersome complaint we observed in the patches being treated with Excimer.

These findings suggest that while Excimer laser therapy enhances the efficacy of topical JAK inhibitors, it also introduces mild and self-limiting side effects.[129] Excimer laser therapy has been found to increase melanocyte stimulation and localized inflammation which could be the possible explanation of the transient adverse events that have been noted including erythema, burning sensation and hyper-pigmentation.[130]

Impact of Clinical Variables on Treatment Response

A. Fitzpatrick Scale

The results indicate a declining trend in treatment response with increasing Fitzpatrick skin scale. Interestingly, the JAK+Excimer group exhibited superior response across all skin types except for Fitzpatrick type II, where the JAK-only group showed better improvement. This suggests that while Excimer laser is beneficial for most patients, its impact may be less pronounced in individuals with lighter skin types. A study by Alikhan et al.[130] noted that lighter skin types respond poorly to all modalities of phototherapy, while another study by Hadi SM et al.[131] observed Fitzpatrick skin types less than III having poor response to Excimer therapy.

B. Lesion Location and Response to Treatment

Lesions on sun-exposed areas, such as the arms and face, exhibited the greatest improvement in VASI scores. This finding supports the hypothesis that UV exposure, even in controlled settings such as Excimer laser therapy, may facilitate repigmentation.[126, 131] In contrast, lesions over acral sites, such as the fingers, and areas over bony prominences, such as the elbows and knees, exhibited the least improvement. These findings are consistent with prior research indicating that vitiligo affecting acral and bony sites is more resistant to treatment.[127]

C. Duration of Disease and Treatment Response

An inverse relationship was observed between disease duration and treatment efficacy. Patients with shorter disease duration demonstrated a more pronounced improvement in VASI scores, whereas those with long-standing vitiligo exhibited a diminished response. This finding is consistent with existing literature, which suggests that earlier intervention in vitiligo leads to better treatment outcomes.[17, 18]Chronic vitiligo is often characterized by melanocyte depletion and fibrosis, which may hinder repigmentation efforts.[132] The greater efficacy observed in the JAK+Excimer group across all disease durations suggests that Excimer laser therapy may mitigate some of these challenges by stimulating residual melanocytes and improving the repigmentation response.[133]

D. Role of Trauma and Family History in Treatment Outcomes

Patients with prior history of trauma demonstrated significantly lower improvement in VASI scores compared to those without trauma history. This negative correlation was more pronounced in the JAK-only group (JAK+Excimer: $r=-0.44$, $p=0.009$; JAK Only: $r=-0.55$, $p=0.0007$). This was in agreement with findings from previous studies, that the Excimer laser may be successful in partially compensating for trauma-associated treatment resistance.[126, 128, 129] Trauma-induced vitiligo is often associated with a more refractory course due to Koebnerization, which may explain the reduced response to treatment.[52, 53]

Family history of vitiligo showed only weak negative correlation with treatment response. While patients with a family history exhibited slightly lower improvement in VASI scores, the association was statistically not significant indicating that family history may not have a substantial impact on treatment efficacy

Clinical Implications and Future Directions

The significantly greater efficacy of concomitant topical Tofacitinib 2% and Excimer therapy compared to Tofacitinib 2% cream alone highlights the potential of combination strategies for optimizing treatment outcomes. Additionally, the significant improvement observed in the JAK-only group underscores the potential of topical Tofacitinib as a standalone treatment option. This is particularly relevant for patients who may not have access to Excimer laser therapy or those who prefer a non-invasive, at-home treatment approach.[2, 3]

Investigating the long-term durability of repigmentation and potential relapse rates following cessation of therapy would also be valuable in guiding clinical decision-making.[17]

CONCLUSION

Both topical JAK inhibitors and combination therapy with Excimer laser are effective in causing re-pigmentation scores in vitiligo patients. The combination therapy exhibited superior efficacy, but it also introduced mild adverse effects. However, these were transient and manageable. Factors such as lesion location, skin type, disease duration, and history of trauma influenced treatment response, emphasizing the need for personalized treatment approaches in vitiligo management. Our findings contribute to the evolving landscape of vitiligo treatment and add to highlight the potential benefits of integrating Excimer laser therapy with JAK inhibitors for enhanced repigmentation outcomes.

Nevertheless, the studies using topical formulations are far and lacking, which is even sparser in case of topical JAK inhibitors such as Tofacitinib. Thus, there is still need for more studies to better understand its efficacy and safety and to determine whether it can be a standalone treatment modality.

SUMMARY

Participants Demographic and Clinical details: The study aimed to evaluate the efficacy of topical Tofacitinib and to compare its effects with and without Excimer laser therapy in patients of vitiligo . total 34 participants with 17 males and 17 females were included in the study. Mean age of study participant was 32.32 years commonest Fitzpatrick skin type was IV amounting to 38.24% followed by type III and IV amounting to 29.41% each. Disease duration varied widely, with a mean of 67.82 months.

Key Findings:

1. Improvement in VASI at 12th week: Both groups, JAK+Excimer and JAK only, showed significant improvement in VASI over 12 weeks. At 12 weeks, VASI scores decreased to 0.043±0.06 in the JAK+Excimer group and 0.059±0.08 in the JAK only group (p=0.477, not significant). However, the overall improvement in VASI was significantly significant (p=0.013) in the JAK+Excimer category (0.7407±0.18) compared to the JAK only group (0.6208±0.25). In the JAK+Excimer group, VASI improvement was significant at all intervals: baseline to 4 weeks (0.868, p=0.006), 4 to 8 weeks (1.059, p=0.001), and 8 to 12 weeks (0.926, p=0.019). In the JAK only group, significant improvement was observed only between weeks 4 to 8 (1.162, p=0.001) and 8 to 12 (0.941, p=0.016), but not in the first 4 weeks (0.500, p=0.11).
2. Treatment Response Based on Clinical Factors: Fitzpatrick skin types III, IV, and V responded better to JAK+Excimer therapy, whereas type II had a better response to JAK only. Lesions in face (JAK+Excimer: 81.17%, JAK only: 79.67%) and arms (JAK+Excimer: 89.50%, JAK only: 80.00%) showed the highest improvement, while those on acral areas like fingers (JAK+Excimer: 47.50%, JAK only: 35.00%) and bony prominences like elbows (JAK+Excimer: 63.20%, JAK only: 39.80%) and knees

(JAK+Excimer: 48.67%, JAK only: 25.73%) showed the least. Disease duration also influenced outcomes, with shorter durations correlating with better responses. Patients without a family history of vitiligo showed greater improvement (JAK+Excimer: 0.7407±0.18, JAK only: 0.6264±0.25, p=0.022), while those with a family history had a weaker response (JAK+Excimer: 0.685±0.16, JAK only: 0.5225±0.24, p=0.248, not significant). A history of trauma before disease onset negatively impacted treatment response, with a moderate negative correlation in the JAK+Excimer group (r=-0.44, p=0.009) and a strong negative correlation in the JAK only group (r=-0.55, p=0.0007).

3. Side Effects: Side effects were observed only in the JAK+Excimer group, including erythema (6 cases, 17.65%), post-inflammatory hyperpigmentation (2 cases, 5.88%), burning sensation (1 case, 2.94%), and desquamation (1 case, 2.94%). All side effects were mild and resolved within 1-2 weeks.

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Annexure-1

INFORMED CONSENT FORM

Title: "COMPARISON BETWEEN EFFICACY OF TOPICAL JAK INHIBITORS AS A MONOTHERAPY VERSUS WITH CONCOMITANT PHOTOTHERAPY IN VITILIGO PATIETNS IN A TERITARY HEALTH CARE CENTRE: A RANDOMISED CONTROLLED TRIAL**"**

Introduction: Vitiligo is an acquired disordered characterised by white patches on the skin affecting 8.8% of Indian. Although the patches are painless and non-itchy, they cause psychological stress, low self esteem and depression for the patient. There are many treatment options available but none have proven to be completely beneficial. A newer modality of treatment in the recent years is the use of JAK inhibitor like Tofacitinib taken as oral medication and topical applicant.

Explanation of procedure: Patients falling under inclusion criteria will be taken for the study. Prior to onset detailed history and examination of the patients will be performed. Vitiligo assessment will be done at baseline using appropriate scales. Patient will be given a tube of Tofacitinib 2% topical applicant (Tofarus Gel 10gm) to apply on 2 selected white patches. One of the 2 selected patches will be treated with Excimer at a frequency of 2times/week. The improvement will be observed using digital photographs and appropriate assessment scales at 4^{th}, 8^{th}, 12^{th}, 16^{th} and 20^{th} weeks.

Withdrawal from participation in the study: Participation in this study in voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will/will not get any benefits by participating in this study. The data gathered will help population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups. However, your identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact: **"**Sneha Ulhaskumar Arakeri, 9148458995, snehaarakeri@gmail.com**"** If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "Comparison between efficacy of topical JAK inhibitors as a mono-therapy versus with concomitant phototherapy in vitiligo patients in a tertiary health care centre: a randomised controlled trial". My signature below

indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

माहिती संमती फॉर्म (Marathi)

Title: "COMPARISON BETWEEN EFFICACY OF TOPICAL JAK INHIBITORS AS A MONOTHERAPY VERSUS WITH CONCOMITANT PHOTOTHERAPY IN VITILIGO PATIETNS IN A TERITARY HEALTH CARE CENTRE: A RANDOMISED CONTROLLED TRIAL"

परिचय: विटिलिगो हा त्वचेचा आजार आहे. हे त्वचेवर पांढरे डाग आहे. याचा परिणाम 8.8% भारतीयांवर होतो. जरी पांढऱ्या डागांना दुखापत झाली आहे आणि त्यात खाज सुटत नाही, परंतु ते मानसिक ताणतणाव, कमी आत्म -सन्मान आणि रुग्णाला नैराश्य देऊ शकतात. यासाठी अनेक उपचार पर्याय उपलब्ध आहेत. परंतु काहीही पूर्णपणे फायदेशीर असल्याचे सिद्ध होत नाही. अलिकडच्या वर्षांत उपचारांची एक नवीन पद्धत म्हणजे टोफासिटिनिब सारख्या जॅक स्टॉपरचा वापर, जो तोंडी औषध आणि मलई घेते.

प्रक्रियेचे स्पष्टीकरणः अभ्यासासाठी समावेशाच्या निकषात पडलेले रुग्ण घेतले जातील. प्रारंभ होण्यापूर्वी तपशीलवार इतिहास आणि रूग्णांची तपासणी केली जाईल. योग्य स्केलचा वापर करून बेसलाइनवर व्हिटिलिगो मूल्यांकन केले जाईल. 2 निवडलेल्या पांढ white ्या पॅचेसवर अर्ज करण्यासाठी रुग्णाला टोफासिटिनिब 2% सामयिक अर्जदार (टोफेरस जेल 10 जीएम) ची एक ट्यूब दिली जाईल. 2 निवडलेल्या 2 पॅचपैकी एक 2 वेळा/आठवड्याच्या वारंवारतेवर एक्झिमरद्वारे उपचार केला जाईल. 4 व्या, 8 व्या, 12 व्या, 16 व्या आणि 20 व्या आठवड्यात डिजिटल छायाचित्रे आणि योग्य मूल्यांकन स्केलचा वापर करून ही सुधारणा पाळली जाईल.

अभ्यासामध्ये सहभागापासून पैसे काढणे: ऐच्छिक मध्ये या अभ्यासामध्ये सहभाग. या अभ्यासामध्ये सहभागी व्हायचे की नाही हे ठरविण्यास आपण मोकळे व्हाल किंवा एकदा नोंदणी केल्यावर सहभाग सुरू ठेवा. आपण आपला सहभाग मागे घेण्याचा निर्णय घेतल्यास, आपण असे करण्यास मोकळे आहात. तथापि, कृपया हा निर्णय मुख्य अन्वेषकांना द्या.

अभ्यासामध्ये भाग घेण्याचे संभाव्य फायदेः या अभ्यासामध्ये भाग घेऊन आपणास कोणतेही फायदे मिळणार नाहीत. गोळा केलेला डेटा मोठ्या प्रमाणात लोकसंख्येस मदत करेल.

अभ्यासामध्ये भाग घेण्यापासून संभाव्य जोखीमः या अभ्यासामध्ये भाग घेण्यात कोणताही धोका नाही.

गोपनीयता आणि गोपनीयता: आपल्याकडून संकलित केलेली माहिती कोडित केली जाईल, कोणत्याही व्यक्तीला आपल्याला ओळखण्यास प्रतिबंधित करण्यासाठी. आपली ओळख कधीही प्रकट होणार नाही. आपल्याकडून गोळा केलेला डेटा गोपनीय ठेवला जाईल आणि केवळ प्रक्रिया किंवा एकत्रित डेटा प्रकाशनासाठी वापरला जाईल.

आर्थिक प्रोत्साहनः या अभ्यासामध्ये भाग घेण्यासाठी आपल्याला कोणतेही देयक प्राप्त होणार नाही.

एकत्रित डेटाच्या प्रकाशनासाठी अधिकृतता: एकत्रित डेटाच्या प्रक्रियेनंतर प्राप्त केलेले परिणाम वैज्ञानिक हेतूसाठी प्रकाशित केले जातील किंवा वैज्ञानिक गटांना सादर केले जातील. तथापि, आपली ओळख कधीही प्रकट होणार नाही.

प्रश्नः या अभ्यासासंदर्भात काही प्रश्न असल्यास, आपण संपर्क साधण्यास मोकळे आहात: "स्नेहा उल्हास्कुमार अराकरी, 9148458995, Snehaarakeri@gmail.com" जर आपल्याला अभ्यासाच्या सहभागाच्या संदर्भात काही प्रश्न किंवा तक्रारी असतील तर आपण संपर्क साधू शकता डॉ. हरशा हेगडे,

अध्यक्ष, जेएनएमसीची नैतिक समिती, 0831-247377777 विस्तार 4052.

कायदेशीर हक्क: या संमती फॉर्मवर स्वाक्षरी करून आम्ही आपले कोणतेही कायदेशीर हक्क लावत नाही

संमती विधान

मी अभ्यासात भाग घेण्याचा एक स्वेच्छेने निर्णय घेत आहे "Comparison between efficacy of topical JAK inhibitors as a mono-therapy versus with concomitant phototherapy in vitiligo patients in a tertiary health care centre: a randomised controlled trial". खाली माझी स्वाक्षरी सूचित करते की मी सहभागी होण्याचे ठरविले आहे आणि मी वर प्रदान केलेली माहिती वाचली आहे किंवा वरील माहिती मला ज्या भाषेत सर्वात चांगली समजली आहे त्या भाषेत मला वाचली गेली आहे. मला प्रश्न विचारण्याची संधी दिली गेली आणि त्यांना माझ्या समाधानाचे उत्तर देण्यात आले.

सहभागींचे नाव:

सहभागींची स्वाक्षरी/डाव्या अंगठा छाप:

साक्षीदाराचे नाव:

साक्षीदाराची स्वाक्षरी/डाव्या अंगठा छाप:

अन्वेषकाचे नाव:

अन्वेषकांची स्वाक्षरी:

ಮಾಹಿತಿಯುತ ಒಪ್ಪಿಗೆ ಫಾರ್ಮ್ (Kannada)

Title: "COMPARISON BETWEEN EFFICACY OF TOPICAL JAK INHIBITORS AS A MONOTHERAPY VERSUS WITH CONCOMITANT PHOTOTHERAPY IN VITILIGO PATIETNS IN A TERITARY HEALTH CARE CENTRE: A RANDOMISED CONTROLLED TRIAL"

ಪರಿಚಯ: ವಿಟಿಲಿಗೊ ಒಂದು ಚರ್ಮದ ಕಾಯಿಲೆ. ಇದು ಚರ್ಮದ ಮೇಲೆ ಬಿಳಿ ಕಲೆಗಳಿಂದ ನಿರೂಪಿಸಲ್ಪಟ್ಟಿದೆ. ಇದು 8.8% ಭಾರತೀಯರ ಮೇಲೆ ಪರಿಣಾಮ ಬೀರುತ್ತದೆ. ಬಿಳಿ ಕಲೆಗಳು ನೋಯಿಸುವ ಮತ್ತು ತುರಿಕೆ ಇಲ್ಲದಿದ್ದರೂ, ಅವು ರೋಗಿಗೆ ಮಾನಸಿಕ ಒತ್ತಡ, ಕಡಿಮೆ ಸ್ವಾಭಿಮಾನ ಮತ್ತು ಖಿನ್ನತೆಗೆ ಕಾರಣವಾಗುತ್ತವೆ. ಇದಕ್ಕಾಗಿ ಅನೇಕ ಚಿಕಿತ್ಸಾ ಆಯ್ಕೆಗಳು ಲಭ್ಯವಿವೆ. ಆದರೆ ಯಾವುದೂ ಸಂಪೂರ್ಣವಾಗಿ ಪ್ರಯೋಜನಕಾರಿ ಎಂದು ಸಾಬೀತಾಗಿಲ್ಲ. ಇತ್ತೀಚಿನ ವರ್ಷಗಳಲ್ಲಿ ಚಿಕಿತ್ಸೆಯ ಒಂದು ಹೊಸ ವಿಧಾನವೆಂದರೆ ಮೌಖಿಕ ಔಷಧಿ ಮತ್ತು ಕ್ರೀಮ್ ಆಗಿ ತೆಗೆದುಕೊಳ್ಳುವ ಟೋಫಾಸಿಟಿನಿಬ್ ನಂತಹ JAK ಪ್ರತಿರೋಧಕದ ಬಳಕೆ.

ಕಾರ್ಯವಿಧಾನದ ವಿವರಣೆ: ಸೇರ್ಪಡೆ ಮಾನದಂಡಗಳ ಅಡಿಯಲ್ಲಿ ಬರುವ ರೋಗಿಗಳನ್ನು ಅಧ್ಯಯನಕ್ಕಾಗಿ ತೆಗೆದುಕೊಳ್ಳಲಾಗುತ್ತದೆ. ಪ್ರಾರಂಭವಾಗುವ ಮೊದಲು ವಿವರವಾದ ಇತಿಹಾಸ ಮತ್ತು ರೋಗಿಗಳ ಪರೀಕ್ಷೆಯನ್ನು ನಡೆಸಲಾಗುತ್ತದೆ. ಸೂಕ್ತವಾದ ಮಾಪಕಗಳನ್ನು ಬಳಸಿಕೊಂಡು ವಿಟಲಿಗೋ ಮೌಲ್ಯಮಾಪನವನ್ನು ಬೇಸ್‌ಲೈನ್‌ನಲ್ಲಿ ಮಾಡಲಾಗುತ್ತದೆ. ಆಯ್ದ 2 ಬಿಳಿ ಪ್ಯಾಚ್‌ಗಳಲ್ಲಿ ಅರ್ಜಿ ಸಲ್ಲಿಸಲು ರೋಗಿಗೆ ಟೊಫಾಸಿಟಿನಿಬ್ 2% ಸಾಮಯಿಕ ಅರ್ಜಿದಾರರ (ಟೊಫರಸ್ ಜೆಲ್ 10 ಗ್ರಾಂ) ಟ್ಯೂಬ್ ನೀಡಲಾಗುತ್ತದೆ. ಆಯ್ದ 2 ಪ್ಯಾಚ್‌ಗಳಲ್ಲಿ ಒಂದನ್ನು ವಾರಕ್ಕೆ 2 ಬಾರಿ ಆವರ್ತನದಲ್ಲಿ ಎಕ್ಸೈಮರ್‌ನೊಂದಿಗೆ ಚಿಕಿತ್ಸೆ ನೀಡಲಾಗುತ್ತದೆ. 4, 8, 12, 16 ಮತ್ತು 20 ನೇ ವಾರಗಳಲ್ಲಿ ಡಿಜಿಟಲ್ s ಾಯಾಚಿತ್ರಗಳು ಮತ್ತು ಸೂಕ್ತವಾದ ಮೌಲ್ಯಮಾಪನ ಮಾಪಕಗಳನ್ನು ಬಳಸಿಕೊಂಡು ಸುಧಾರಣೆಯನ್ನು ಗಮನಿಸಬಹುದು.

ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯಿಂದ ಹಿಂತೆಗೆದುಕೊಳ್ಳುವಿಕೆ: ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಬೇಕೆ ಅಥವಾ ಒಮ್ಮೆ ದಾಖಲಾದ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ಮುಂದುವರಿಸಬೇಕೆ ಎಂದು ನಿರ್ಧರಿಸಲು ನೀವು ಮುಕ್ತರಾಗುತ್ತೀರಿ. ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ಹಿಂತೆಗೆದುಕೊಳ್ಳಲು ನೀವು ನಿರ್ಧರಿಸಿದರೆ, ನೀವು ಹಾಗೆ ಮಾಡಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ. ಆದಾಗ್ಯೂ, ದಯವಿಟ್ಟು ನಿರ್ಧಾರವನ್ನು ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿಗೆ ತಿಳಿಸಿ.

ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದರಿಂದ ಸಂಭವನೀಯ ಪ್ರಯೋಜನಗಳು: ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವ ಮೂಲಕ ನೀವು ಯಾವುದೇ ಪ್ರಯೋಜನಗಳನ್ನು ಪಡೆಯುವುದಿಲ್ಲ/ಪಡೆಯುವುದಿಲ್ಲ. ಸಂಗ್ರಹಿಸಿದ ದತ್ತಾಂಶವು ಜನಸಂಖ್ಯೆಗೆ ದೊಡ್ಡದಾಗಿ ಸಹಾಯ ಮಾಡುತ್ತದೆ.

ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದರಿಂದ ಸಂಭವನೀಯ ಅಪಾಯಗಳು: ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಲ್ಲಿ ಯಾವುದೇ ಅಪಾಯಗಳಿಲ್ಲ.

ಗೌಪ್ಯತೆ ಮತ್ತು ಗೌಪ್ಯತೆ: ನಿಮ್ಮನ್ನು ಗುರುತಿಸಲು ಯಾವುದೇ ವ್ಯಕ್ತಿಯನ್ನು ತಡೆಯಲು ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಕೋಡ್ ಮಾಡಲಾಗುತ್ತದೆ. ನಿಮ್ಮ ಗುರುತು ಎಂದಿಗೂ ಬಹಿರಂಗಗೊಳ್ಳುವುದಿಲ್ಲ. ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಡೇಟಾವನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುತ್ತದೆ ಮತ್ತು ಸಂಸ್ಕರಿಸಿದ ಅಥವಾ ಒಟ್ಟು ಡೇಟಾವನ್ನು ಮಾತ್ರ ಪ್ರಕಟಣೆಗೆ ಬಳಸಲಾಗುತ್ತದೆ.

ಹಣಕಾಸಿನ ಪ್ರೋತ್ಸಾಹ: ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಯಾವುದೇ ಪಾವತಿಯನ್ನು ಸ್ವೀಕರಿಸುವುದಿಲ್ಲ.

ಒಟ್ಟು ಡೇಟಾವನ್ನು ಪ್ರಕಟಿಸಲು ಒಪ್ಪಿಗೆ: ಒಟ್ಟು ಡೇಟಾವನ್ನು ಪ್ರಕ್ರಿಯೆಗೊಳಿಸಿದ ನಂತರ ಪಡೆದ ಫಲಿತಾಂಶಗಳನ್ನು ವೈಜ್ಞಾನಿಕ ಉದ್ದೇಶಕ್ಕಾಗಿ ಪ್ರಕಟಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ವೈಜ್ಞಾನಿಕ ಗುಂಪುಗಳಿಗೆ ಪ್ರಸ್ತುತಪಡಿಸಲಾಗುತ್ತದೆ. ಆದಾಗ್ಯೂ, ನಿಮ್ಮ ಗುರುತು ಎಂದಿಗೂ ಬಹಿರಂಗಗೊಳ್ಳುವುದಿಲ್ಲ.

ಪ್ರಶ್ನೆಗಳು: ಈ ಅಧ್ಯಯನಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ ಯಾವುದೇ ಪ್ರಶ್ನೆಗಳ ಸಂದರ್ಭದಲ್ಲಿ, ನೀವು

ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ: "ಸ್ನೆಹಾ ಉಲ್ಹಾಸ್ಕುಮಾರ್ ಅರೇಕೆರಿ, 9148458995, snehaaarakeri@gmail.com" ನಿಮ್ಮ ಹಕ್ಕಿಗೆ ಸಂಬಂಧಿಸಿದಂತೆ ನೀವು ಯಾವುದೇ ಪ್ರಶ್ನೆ ಅಥವಾ ದೂರುಗಳನ್ನು ಹೊಂದಿದ್ದರೆ ಅಧ್ಯಯನ ಭಾಗವಹಿಸುವವರಂತೆ ನೀವು ಸಂಪರ್ಕಿಸಬಹುದು ಡಾ. ಹರ್ಷಾ ಹೆಗ್ಡೆ, ಅಧ್ಯಕ್ಷರು, ಜೆಎನ್ಎಂಸಿಯ ನೈತಿಕ ಸಮಿತಿ, 0831-2473777 ವಿಸ್ತರಣೆ 4052.

ಕಾನೂನು ಹಕ್ಕುಗಳು: ಈ ಒಪ್ಪಿಗೆ ಫಾರ್ಮ್‌ಗೆ ಸಹಿ ಹಾಕುವ ಮೂಲಕ, ನಾವು ನಿಮ್ಮ ಯಾವುದೇ ಕಾನೂನು ಹಕ್ಕುಗಳನ್ನು ಬೀಸುತ್ತಿಲ್ಲ

ಒಪ್ಪಿಗೆ ಹೇಳಿಕೆ

ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನಾನು ಸ್ವಯಂಪ್ರೇರಿತ ನಿರ್ಧಾರವನ್ನು ತೆಗೆದುಕೊಳ್ಳುತ್ತಿದ್ದೇನೆ "Comparison between efficacy of topical JAK inhibitors as a mono-therapy versus with concomitant phototherapy in vitiligo patients in a tertiary health care centre: a randomised controlled trial". ಕೆಳಗಿನ ನನ್ನ ಸಹಿ ನಾನು ಭಾಗವಹಿಸಲು ನಿರ್ಧರಿಸಿದೆ ಎಂದು ಸೂಚಿಸುತ್ತದೆ ಮತ್ತು ಮೇಲೆ ಒದಗಿಸಿದ ಮಾಹಿತಿಯನ್ನು ನಾನು ಓದಿದ್ದೇನೆ ಅಥವಾ ಮೇಲೆ ಒದಗಿಸಿದ ಮಾಹಿತಿಯನ್ನು ನಾನು ಚೆನ್ನಾಗಿ ಅರ್ಥಮಾಡಿಕೊಳ್ಳುವ ಭಾಷೆಯಲ್ಲಿ ನನಗೆ ಓದಿದ್ದೇನೆ. ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನಗೆ ಅವಕಾಶ ನೀಡಲಾಯಿತು ಮತ್ತು ನನ್ನ ತೃಪ್ತಿಗೆ ಅವರಿಗೆ ಉತ್ತರಿಸಲಾಗಿದೆ.

ಭಾಗವಹಿಸುವವರ ಹೆಸರು:

ಭಾಗವಹಿಸುವವರ ಸಹಿ/ಎಡ ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆ:

ಸಾಕ್ಷಿಯ ಹೆಸರು:

ಸಾಕ್ಷಿಯ ಸಹಿ/ಎಡ ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆ:

ತನಿಖಾಧಿಕಾರಿಯ ಹೆಸರು:

ತನಿಖಾಧಿಕಾರಿಯ ಸಹಿ:

<u>सूचित सहमति प्रपत्र (Hindi)</u>

Title: "COMPARISON BETWEEN EFFICACY OF TOPICAL JAK INHIBITORS AS A MONOTHERAPY VERSUS WITH CONCOMITANT PHOTOTHERAPY IN VITILIGO PATIETNS IN A TERITARY HEALTH CARE CENTRE: A RANDOMISED CONTROLLED TRIAL"

परिचय: विटिलिगो एक त्वचा रोग है। यह त्वचा पर सफेद धब्बों है। यह 8.8% भारतीयों को प्रभावित करता है। यद्यपि सफेद धब्बे आहत होते हैं और कोई खुजली नहीं होती है, वे रोगी के लिए मानसिक तनाव, कम आत्म -आत्मसम्मान और अवसाद का कारण बन सकते हैं। इसके लिए कई उपचार विकल्प उपलब्ध हैं। लेकिन कुछ भी पूरी तरह से फायदेमंद साबित नहीं होता है। हाल के वर्षों में उपचार की एक नई विधि एक JAK रोकनेवाला का उपयोग है, जैसे कि टोफासिटिनिब, जो मौखिक दवा और क्रीम में ले जाता है।

प्रक्रिया का स्पष्टीकरण: समावेशन मानदंडों के तहत आने वाले मरीजों को अध्ययन के लिए लिया जाएगा। शुरुआत से पहले विस्तृत इतिहास और रोगियों की परीक्षा का प्रदर्शन किया जाएगा। विटिलिगो का मूल्यांकन उचित पैमानों का उपयोग करके बेसलाइन पर किया जाएगा। रोगी को 2 चयनित सफेद पैच पर लागू करने के लिए टोफैसिटिनिब 2% सामयिक आवेदक (टोफारस जेल 10 ग्राम) की एक ट्यूब दी जाएगी। 2 चयनित पैच में से एक को 2Times/सप्ताह की आवृत्ति पर एक्साइमर के साथ व्यवहार किया जाएगा। 4, 8 वें, 12 वें, 16 वें और 20 वें सप्ताह में डिजिटल तस्वीरों और उचित मूल्यांकन तराजू का उपयोग करके सुधार देखा जाएगा।

अध्ययन में भागीदारी से वापसी: स्वैच्छिक में इस अध्ययन में भागीदारी। आप यह तय करने के लिए स्वतंत्र होंगे कि इस अध्ययन में भाग लेना है या एक बार दाखिला लेने के बाद भागीदारी जारी रखें। यदि आप अपनी भागीदारी को वापस लेने का निर्णय लेते हैं, तो आप ऐसा करने के लिए स्वतंत्र हैं। हालांकि, कृपया प्रमुख अन्वेषक को निर्णय लें।

अध्ययन में भाग लेने से संभावित लाभ: इस अध्ययन में भाग लेने से आपको कोई लाभ नहीं मिलेगा। एकत्र किए गए डेटा से जनसंख्या में बड़े पैमाने पर मदद मिलेगी।

अध्ययन में भाग लेने से संभावित जोखिम: इस अध्ययन में भाग लेने में कोई जोखिम शामिल नहीं हैं।

गोपनीयता और गोपनीयता: आप से एकत्र की गई जानकारी को कोडित किया जाएगा, ताकि किसी भी व्यक्ति को आपकी पहचान करने से रोका जा सके। आपकी पहचान कभी सामने नहीं आएगी। आपसे एकत्र किए गए डेटा को गोपनीय रखा जाएगा और केवल संसाधित या एकत्रित डेटा का उपयोग प्रकाशन के लिए किया जाएगा।

वित्तीय प्रोत्साहन: आपको इस अध्ययन में भाग लेने के लिए कोई भुगतान नहीं मिलेगा।

एकत्रित डेटा के प्रकाशन के लिए प्राधिकरण: एकत्रित डेटा के प्रसंस्करण के बाद प्राप्त परिणाम वैज्ञानिक उद्देश्य के लिए प्रकाशित किए जाएंगे और वैज्ञानिक समूहों को प्रस्तुत किए जाएंगे। हालाँकि, आपकी पहचान कभी सामने नहीं आएगी।

प्रश्न: इस अध्ययन के संबंध में किसी भी प्रश्न के मामले में, आप संपर्क करने के लिए स्वतंत्र हैं: "स्नेहा उलहस्कुमार अरेकेरी, 9148458995, snehaarakeri@gmail.com" यदि आपके पास अध्ययन प्रतिभागी के रूप में अपने अधिकार के संबंध में कोई प्रश्न या शिकायत है, तो आप संपर्क कर सकते हैं डॉ। हर्ष हेगडे, चेयरपर्सन, जेएनएमसी की नैतिक समिति, 0831-2473777 एक्सटेंशन 4052।

कानूनी अधिकार: इस सहमति फॉर्म पर हस्ताक्षर करके, हम आपके किसी भी कानूनी अधिकार को

नहीं लहरा रहे हैं

सहमति विवरण

मैं अध्ययन में भाग लेने के लिए एक स्वैच्छिक निर्णय ले रहा हूं "Comparison between efficacy of topical jak inhibitors as a monotherapy versus with concomitant phototherapy in vitiligo patietns in a teritary health care centre: a randomised controled trial"। नीचे दिए गए मेरा हस्ताक्षर इंगित करता है कि मैंने भाग लेने का फैसला किया है और मैंने ऊपर दी गई जानकारी को पढ़ा है या ऊपर दी गई जानकारी मुझे उस भाषा में पढ़ी गई है जिसे मैं सबसे अच्छा समझता हूं। मुझे सवाल पूछने का अवसर दिया गया और उन्हें मेरी संतुष्टि का जवाब दिया गया।

प्रतिभागी का नाम:

प्रतिभागी के हस्ताक्षर/बाएं अंगूठे की छाप:

गवाह का नाम:

गवाह के हस्ताक्षर/बाएं अंगूठे की छाप:

अन्वेषक का नाम:

अन्वेषक का हस्ताक्षर:

Annexure-2

PROFORMA

TITLE: A COMPARISON BETWEEN EFFICACY OF TOPICAL JAK INHIBITORS ALOEN VS TOPICAL JAK INHIBITOR WITH PHOTOTHERAPY IN VITILIGO PATIETNS IN A TERITARY HEALTH CARE CENTRE: AN OPEN LABELLED STUDY

DEMOGRAPHIC DETAILS

NAME			
AGE			
SEX	MALE	FEMALE	
OCCUPATION	EMPLOYED	UNEMPLOYED	
DATE			
ADDRESS			
DURATION OF DISEASE	MONTHS	YEARS	
HISTORY OF ONSET			
EXPOSURE TO SUNLIGHT	PRESENT (MINS/DAY)	ABSENT	
PAST HISTORY			
TREATMENT HISTORY	MODALITY	MONTHS	RESPONSE
	1.		
	2.		
	3.		
	4.		
FAMILY HISTORY			
FITZPATRICK SKIN TYPE			

GENERAL PHYSICAL EXAMINATION

PR	BP	Weight	Height	BMI
PALLOR □ ICTERUS □ CLUBBING □ CYANOSIS □ LYMPHADENOPATHY □ EDEMA □				

VASI

	BASELINE	4th WEEK	8th WEEK	12th WEEK
LESION 1 (TOPICAL TOFACITINIB)				
LESION 2 (TOPICAL TOFACITINIB + EXCIMER)				

VITILIGO EUROPEAN TASK FORCE SCORING

	BASELINE	4th WEEK	8th WEEK	12th WEEK
LESION 1 (TOPICAL TOFACITINIB)				
LESION 2 (TOPICAL TOFACITINIB + EXCIMER)				

Annexure-2
PHOTOGRAPHS

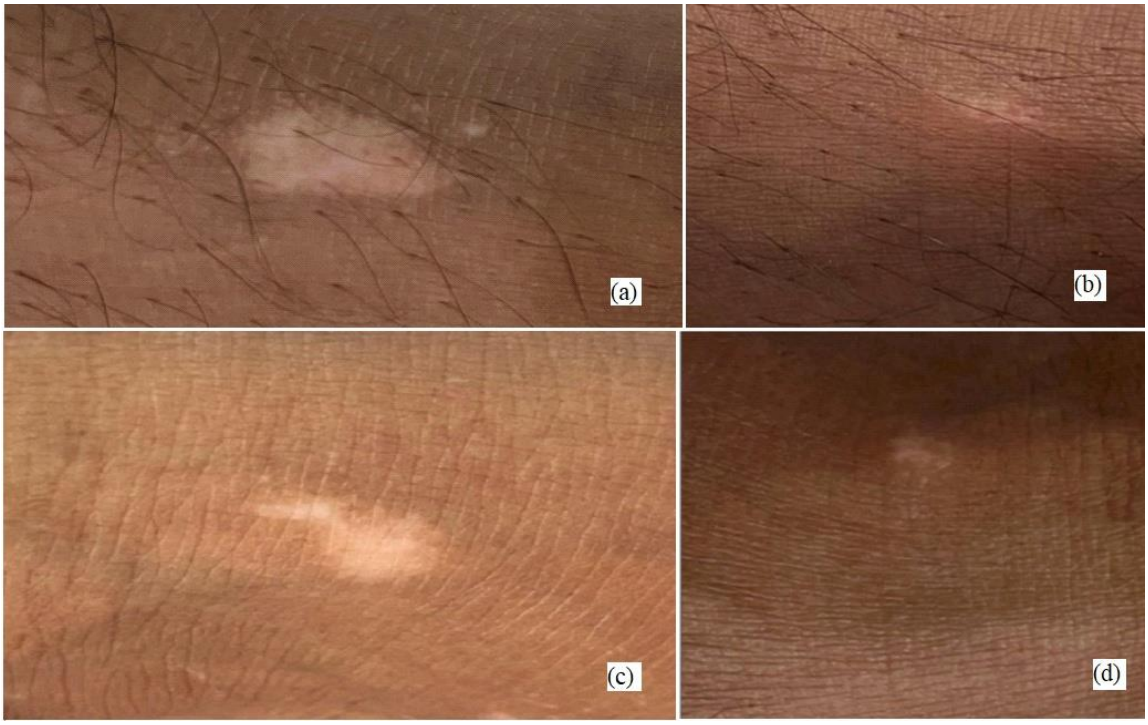

Figure 1: (a) Lesion over left arm treated with JAK+Excimer at baseline with VASI of 0.01 and (b) at 12 weeks with VASI reduced to 0.0013. (c) Lesion over right arm treated with JAK only at baseline with VASI of 0.01 and (d) at 12 weeks with VASI reduced to 0.002

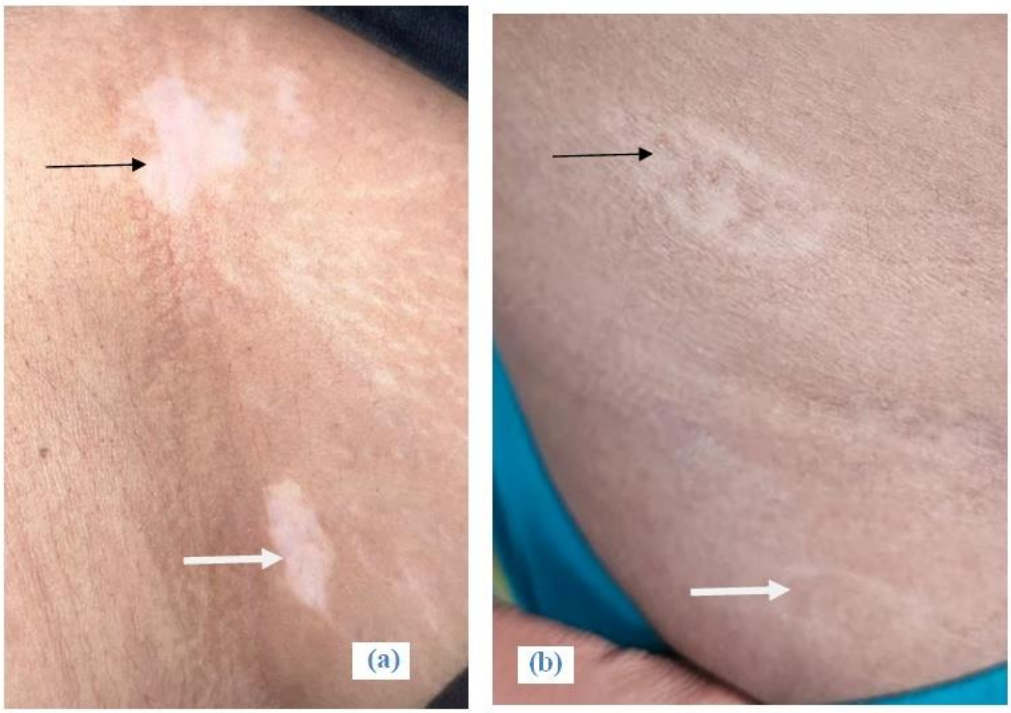

Figure 2: (a) Lesions over abdomen at baseline with upper lesion (black arrow) showing VASI of 0.2 and was treated with topical JAK only and the lower lesion (white arrow) treated with JAK+Excimer showing VASI 0.25. (b) Lesion at 12th week with upper lesion (black arrow) showing improved VASI of 0.02 and the lower lesion (white arrow) showing VASI of 0.062.

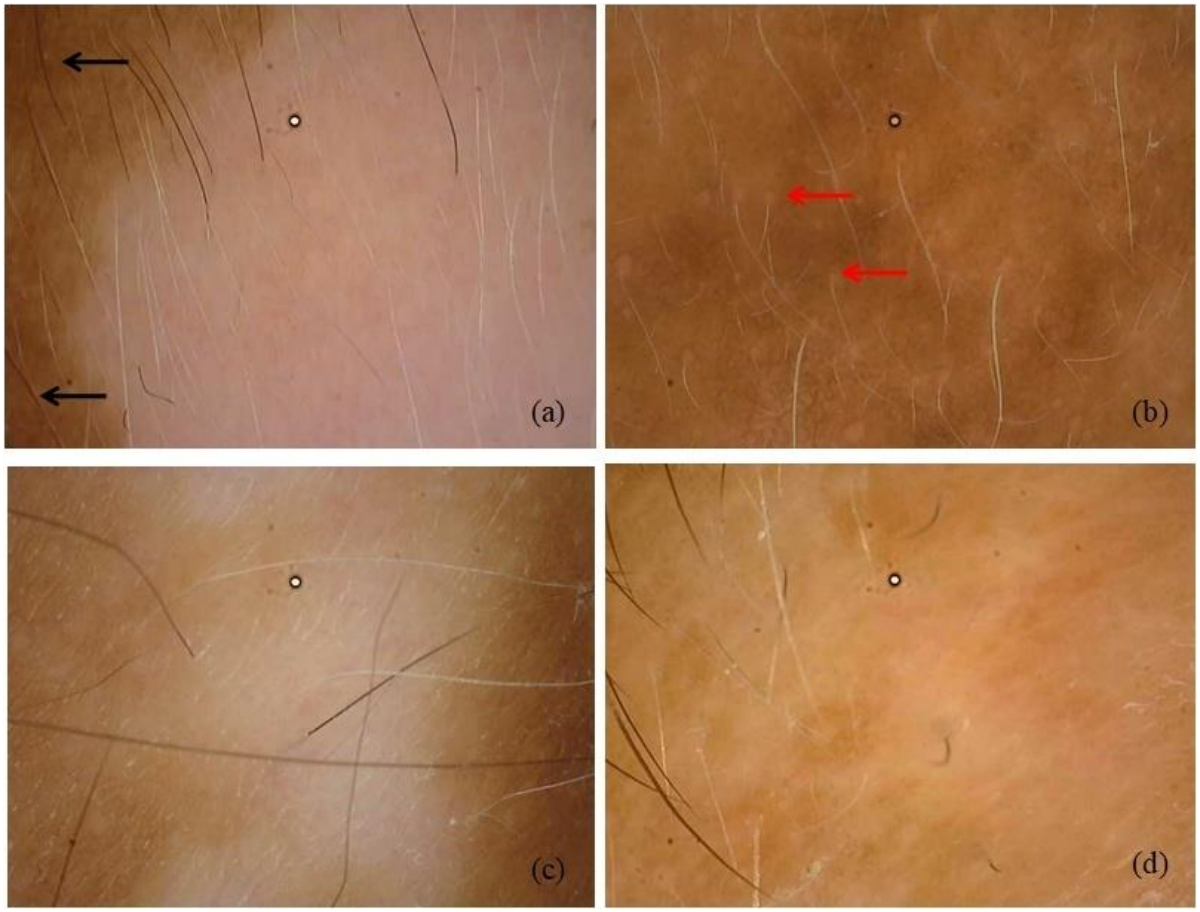

Figure 3: (a) A lesion over left side of face treated with JAK+Excimer at baseline showing absent pigment network and leukotrichia with few satellite lesions (black arrow) and (b) at 12 weeks showing normal pigment network and areas of peri-follicular hypo-pigmentation (red arrow) and persistence of leukotrichia with VASI reduced to 0.0013. (c) A lesion over right side of face of same patient treated with JAK only at baseline showing absent pigment network, starburst pattern, and leukotrichia and (d) at 12 weeks showing reduced pigment network, few intra- and peri-lesional areas of normal pigmentation and persistence of leukotrichia.

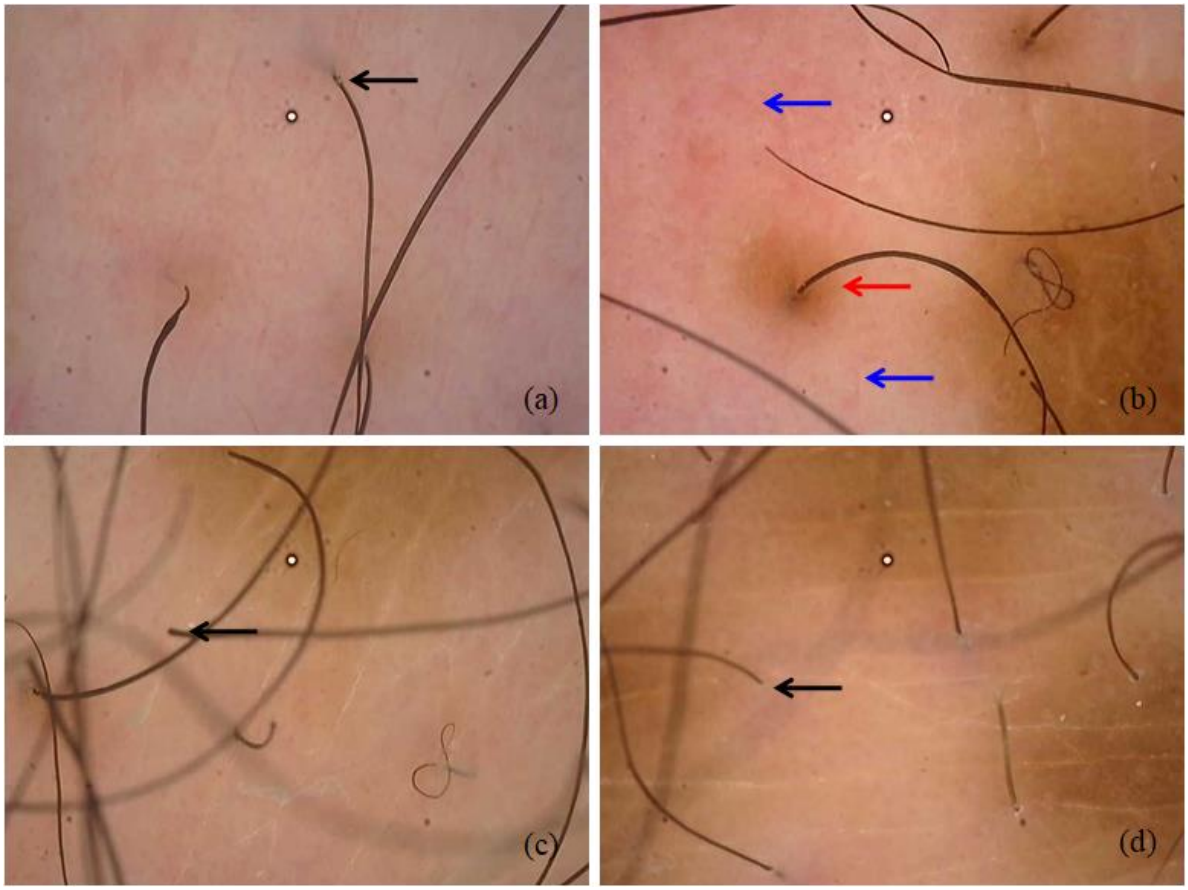

Figure 4: (a) A lesion over left leg treated with JAK+Excimer at baseline showing reduced pigment network and peri-follicular de-pigmentation (black arrow) and (b) at 12 weeks showing persistence of reduced pigment network along with peri-follicular hyperpigmentation (red arrow), erythema, telangiectasia(blue arrow) and reduced size of the lesion. (c) A lesion right leg treated with JAK only at baseline showing absent pigment network and peri-follicular de-pigmentation (black arrow) and (d) at 12 weeks showing persistence of absent pigment network and peri-follicular de-pigmentation (black arrow) along with peri-lesional areas of hyper-pigmentation and reduced size of the lesion.

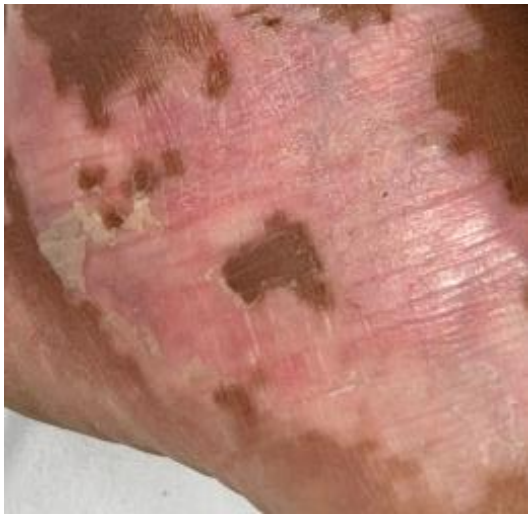

Figure 5: Erythema after 1st sitting of Excimer laser on a lesion over medial aspect of ankle was associated with burning sensation

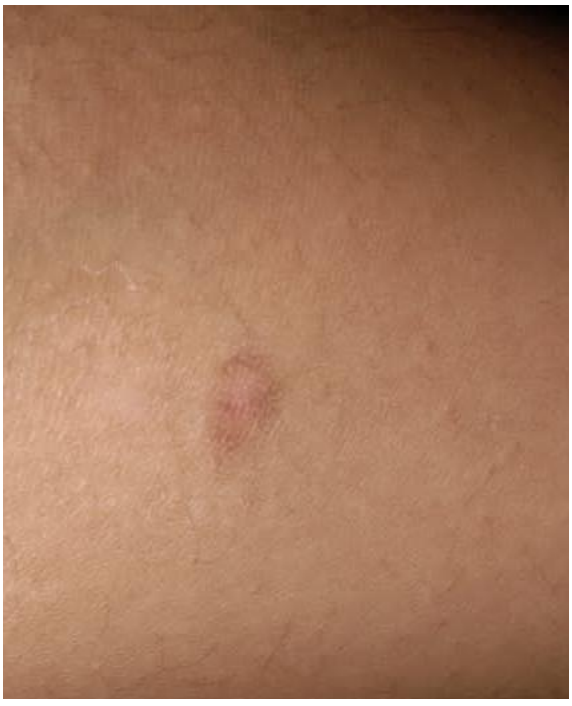

Figure 6: Hyperpigmentation at Excimer site in a lesion over flexor aspect of forearm after 12 weeks of treatment with Excimer laser showing hyperpigmentation

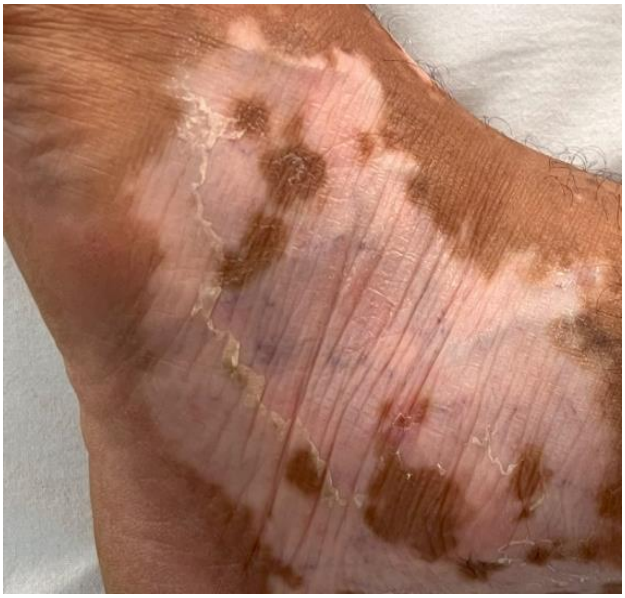

Figure 7: Desquamation of skin seen after 2 sittings of Excimer laser over medial aspect of the ankle

Annexure-4
MASTERCHART

Sr. No.	Name	OP No.	Age (years)	Sex (M/F)	Address	Fitzpatrick skin type (I-VI)	Duration of Disease (Months)	Location of disease	H/O trauma prior to onset (Y/N)	Treatment History	Family History (Y/N)
1	Aishwarya(1)	7120616	26	F	Bailhongal	III	12	Abdomen	N	1.Weeknd Betamethasone 4mg (tapered down) 2.Topical Tacrolimus 3.Topical Psoraline 4.Hand-held NBUVB	N
2	Aishwarya (2)	7120616	26	F	Bailhongal	III	12	Ankles	Y	1.Weeknd Betamethasone 4mg (tapered down) 2.Topical Tacrolimus 3.Topical Psoraline 4.Hand-held NBUVB	N
3	Asma (1)	7327066	42	F	Mudhol	III	4	Elbows	N	1.T Apremilast 30mg	Y
4	Bhimappa	7335028	45	M	Kanaratti	IV	5	Face	N	1.Topical Fluticasone	N
5	Gangavva	7342605	66	F	Yellapur	V	>360	Neck	N	-	Y
6	Goutam (1)	7296494	15	M	Belagavi	IV	48	Face	N	1.Topical Psoralines	N
7	Goutam (2)	7296494	15	M	Belagavi	IV	48	Shins	N	1.Topical Psoralines	N
8	Akshata (1)	6165784	23	F	Kittur	IV	7	Abdomen	N	1.T Azathioprine 50mg 2.Weekend Betamethasone 3mg (tapered down) 3.Topical Tacrolimus 4.NBUVB	Y
9	Akshata (2)	6165784	23	F	Kittur	IV	7	Ankles	N	1.T Azathioprine 50mg 2.Weekend Betamethasone 3mg (tapered down) 3.Topical Tacrolimus 4.NBUVB	Y
10	Gurunath (1)	3390069	31	M	Tarihal	IV	180	Knees	Y	1.Weekend Betamethasone 3mg (tapered down) 2. NBUVB	N
11	Gurunath (2)	3390069	31	M	Tarihal	IV	180	Elbows	N	1.Weekend Betamethasone 3mg (tapered down) 2. NBUVB	N
12	Gurunath (3)	3390069	31	M	Tarihal	IV	180	Knees	Y	1.Weekend Betamethasone 3mg (tapered down) 2. NBUVB	N
13	Kalyani (1)	6851779	47	F	Chikkodi	V	36	Elbows	N	1.Oral Tofacitinib 2.Topical Tacrolimus 3.NBUVB	N
14	Kalyani (2)	6851779	47	F	Chikkodi	V	36	Elbows	N	1.Oral Tofacitinib 2.Topical Tacrolimus 3.NBUVB	N
15	Manish (1)	1408876	54	M	Belagavi	V	3	Face	N	-	N

16	Manish (2)	1408876	54	M	Belagavi	V	3	Abdomen	N	-	N
17	Manjunath (1)	5169062	43	M	Belagavi	V	52	Hands	Y	1.T Azathioprine 50mg 2.Weekend Betamethasone 3mg (tapered down) 3.Topical Tacrolimus 4.NBUVB	N
18	Manjunath (2)	5169062	43	M	Belagavi	V	52	Feet	N	1.T Azathioprine 50mg 2.Weekend Betamethasone 3mg (tapered down) 3.Topical Tacrolimus 4.NBUVB	N
19	Manjunath (3)	5169062	43	M	Belagavi	V	52	Shins	N	1.T Azathioprine 50mg 2.Weekend Betamethasone 3mg (tapered down) 3.Topical Tacrolimus 4.NBUVB	N
20	Prakash (1)	7127160	22	M	Belagavi	III	9	Shins	N	-	N
21	Prakash (2)	7127160	22	M	Belagavi	III	9	Knees	N	-	N
22	Priya (1)	6801970	28	F	Chikkodi	III	240	Forearm	N	-	N
23	Priya (2)	6801970	28	F	Chikkodi	III	240	Chest	N	-	N
24	Rajendra	6423208	52	M	Belagavi	V	12	Fingers	Y	-	N
25	Ramangouda (1)		15	F	Belagavi	III	240	Elbows	N	1.T Tofacitinib 5mg 2.Weekend Betamethasone 3mg (tapered down) 3.Topical Tacrolimus 4.NBUVB	N
26	Ramangouda (2)		15	F	Belagavi	III	240	Feet	N	1.T Tofacitinib 5mg 2.Weekend Betamethasone 3mg (tapered down) 3.Topical Tacrolimus 4.NBUVB	N
27	Ratna	7294073	27	F	Belagavi	V	36	Face	N	1. Topical Mometasone 2. NBUVB	N
28	Sangeeta	6244271	37	F	Belagavi	III	15	Ankles	N	-	N
29	Sanvi (B/O Shruti)	4243769	15	F	Belagavi	II	4	Face	N	-	N
30	Shravani (1)	7083359	16	F	Belagavi	IV	76	Ankles	N	1. Weekend Betamethasone 3mg (tapered down) 2. Topical Tacrolimus	N
31	Shravani (2)	7083359	16	F	Belagavi	IV	76	Foot	N	1. Weekend Betamethasone 3mg (tapered down) 2. Topical Tacrolimus	N
32	Sudheer	5376370	22	M	Belagavi	V	38	Foot	N	-	N
33	Sudheer	5376370	22	M	Belagavi	V	38	Face	N	-	N
34	Yesayya	4783087	57	M	Belagavi	V	48	Fingers	Y	1.Weeknd Betamethasone 4mg (tapered down) 2.Topical Tacrolimus 3.Topical Psoraline	N

VASI														Improvement at week 12		Adverse Effects
Baseline (BSA)		4th week				8th week				12th week						
JAK+ Excimer	JAK Only	JAK+ Excimer	Diff.	JAK Only	Diff.	JAK+ Excimer	Diff.	JAK Only	Diff.	JAK+ Excimer	Diff.	JAK Only	Diff.	JAK+ Excimer	JAK Only	
0.083	0.25	0.075	0.096386	0.225	0.1	0.033	0.60241	0.175	0.3	0.0083	0.9	0.062	0.752	90%	75%	Erythema (Excimer site)
0.112	0.059	0.1	0.107143	0.059	0	0.062	0.446429	0.056	0.0508	0.017	0.84821	0.031	0.4746	85%	48%	-
0.05	0.015	0.038	0.24	0.015	0	0.033	0.34	0.014	0.0667	0.013	0.74	0.009	0.4	74%	40%	-
0.25	0.25	0.188	0.248	0.2	0.2	0.138	0.448	0.163	0.348	0.025	0.9	0.062	0.752	90%	75%	1. Erythema (Excimer site) 2. Acne flare at 2nd week pf study
0.2	0.225	0.16	0.2	0.2	0.11111	0.09	0.55	0.1625	0.2778	0.03	0.85	0.05	0.7778	85%	78%	Erythema and burning sensation (Excimer site)
0.3	0.2	0.24	0.2	0.17	0.15	0.165	0.45	0.11	0.45	0.045	0.85	0.04	0.8	85%	80%	-
1	1	0.825	0.175	1	0	0.5	0.5	0.75	0.25	0.15	0.85	0.25	0.75	85%	75%	-
0.05	0.09	0.05	0	0.06	0.33333	0.03	0.4	0.06	0.3333	0.025	0.5	0.06	0.3333	50%	33%	Post-inflamatory hyperpigmentation (Excimer site)
0.075	0.015	0.075	0	0.013	0.13333	0.025	0.666667	0.005	0.6667	0.01	0.86667	0.003	0.8	87%	80%	-
0.188	0.24	0.188	0	0.24	0	0.125	0.335106	0.24	0	0.1	0.46809	0.225	0.0625	47%	6%	Erythema and burning sensation (Excimer site)
0.225	0.125	0.15	0.333333	0.125	0	0.12	0.466667	0.1	0.2	0.09	0.6	0.088	0.296	60%	30%	-
0.09	0.075	0.075	0.166667	0.075	0	0.075	0.166667	0.07	0.0667	0.06	0.33333	0.07	0.0667	33%	7.00%	-
0.05	0.05	0.05	0	0.05	0	0.0375	0.25	0.05	0	0.03	0.4	0.04	0.2	40%	20%	-
0.18	0.3	0.18	0	0.3	0	0.15	0.166667	0.24	0.2	0.08	0.55556	0.2	0.3333	56%	33%	Post-inflamatory hyperpigmentation (Excimer site)- after 8th week (resolved later)
0.045	0.063	0.034	0.244444	0.056	0.11111	0.03	0.333333	0.042	0.3333	0.01	0.77778	0.0175	0.7222	78%	72%	-

0.5	0.45	0.375	0.25	0.375	0.16667	0.25	0.5	0.325	0.2778	0.05	0.9	0.1	0.7778	90%	78%	Post-inflamatory hyperpigmentation (Excimer site)
0.114	0.06	0.08	0.298246	0.06	0	0.048	0.578947	0.042	0.3	0.024	0.78947	0.024	0.6	79%	60%	-
0.9	0.8	0.8	0.111111	0.8	0	0.62	0.311111	0.55	0.3125	0.225	0.75	0.175	0.7813	75%	78%	1.Desquamation (Excimer site) 2. Erythema (excimer site)
1.02	0.9	0.95	0.068627	0.9	0	0.6375	0.375	0.75	0.1667	0.25	0.7549	0.3	0.6667	75%	67%	-
0.45	0.18	0.35	0.222222	0.15	0.16667	0.25	0.444444	0.12	0.3333	0.1	0.77778	0.08	0.5556	78%	56%	
0.18	0.125	0.16	0.111111	0.125	0	0.12	0.333333	0.1	0.2	0.06	0.66667	0.045	0.64	66%	64%	-
0.04	0.04	0.04	0	0.025	0.375	0	1	0	1	0	1	0	1	100%	100%	Post-inflamatory hyperpigmentation (Excimer site)
0.05	0.075	0.04	0.2	0.065	0.13333	0.025	0.5	0.045	0.4	0.01	0.8	0.015	0.8	80%	80%	-
0.01	0.0075	0.008	0.2	0.007	0.06667	0.0055	0.45	0.0055	0.2667	0.0025	0.75	0.003	0.6	75%	60%	-
0.09	0.075	0.08	0.111111	0.075	0	0.055	0.388889	0.06	0.2	0.0125	0.86111	0.0175	0.7667	86%	76.00%	-
0.045	0.05	0.04	0.111111	0.05	0	0.025	0.444444	0.045	0.1	0.0075	0.83333	0.01	0.8	83%	80%	Post-inflamatory hyperpigmentation (Excimer site)
0.008	0.01	0.007	0.125	0.01	0	0.0055	0.3125	0.0075	0.25	0.0025	0.6875	0.0025	0.75	69%	75%	Post inflamatory hyperpigmentation worsened (excimer site)
0.01	0.01	0.0075	0.25	0.008	0.2	0.006	0.4	0.005	0.5	0.001	0.9	0.0015	0.85	90%	85%	-
0.01	0.005	0.008	0.2	0.002	0.6	0.0065	0.35	0	1	0.002	0.8	0	1	80%	100%	-
0.05	0.04	0.045	0.1	0.04	0	0.025	0.5	0.0275	0.3125	0.01	0.8	0.0115	0.7125	80%	71%	-
0.02	0.02	0.0125	0.375	0.0175	0.125	0.005	0.75	0.01	0.5	0.005	0.75	0.0075	0.625	75%	62%	-
0.01	0.01	0.0075	0.25	0.01	0	0.0015	0.85	0.002	0.8	0.00125	0.875	0.002	0.8	87%	80%	-
0.03	0.025	0.025	0.166667	0.02	0.2	0.01	0.666667	0.015	0.4	0.0045	0.85	0.006	0.76	85%	76%	Erythema (Excimer site)
0.01	0.01	0.008	0.2	0.01	0	0.008	0.2	0.01	0	0.008	0.2	0.009	0.1	20%	10%	Erythema (Excimer site)