"A COMPARATIVE RANDOMISED CLINICAL TRIAL TO DETERMINE THE EFFICACY OF 308nm EXCIMER LAMP VS TOPICAL FLUTICASONE CREAM IN THE TREATMENT OF ALOPECIA AREATA"

Submitted by

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M.D.

In

DERMATOLOGY, VENEREOLOGY AND LEPROSY

UNDER THE GUIDANCE OF

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I hereby declare that this dissertation entitled **"A COMPARATIVE RANDOMISED CLINICAL TRIAL TO DETERMINE THE EFFICACY OF 308nm EXCIMER LAMP VS TOPICAL FLUTICASONE CREAM IN THE TREATMENT OF ALOPECIA AREATA"** is a bonafide and genuine research work carried out by me under the guidance of **DR. ARUN C. INAMADAR.,** Professor and HOD, Department of Dermatology, Venereology and Leprosy at BLDE University's Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapur.

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LIST OF ABBREVIATIONS

1. AA : Alopecia Areata
2. AT : Alopecia totalis
3. AU : Alopecia universalis
4. PUVA : Psoralen plus ultraviolet A
5. NBUVB : Narrowband ultraviolet B
6. UV : Utraviolet
7. GWAS : Genome wide association studies
8. TGF-β : Transforming growth factor beta
9. IGF-1 : Insulin like growth factor 1
10. ICAM-2 : Intracellular adhesion molecule 2
11. ELAM-1 : Endothelial cell leukocyte adhesion molecule 1
12. α-MSH : Alpha melanocyte stimulating harmone
13. MHC : Major histocompatibility complex
14. APC : Antigen presenting cells
15. HLA : Human leukocyte antigen
16. HPA: Hypothalamic-pituitary-adrenal
17. MIF : Macrophage migration inhibitory factor
18. DPCP : Diphenylcyclopropenone
19. SADBE : Squaric acid dibutylester
20. OMP : Oral mini pluse
21. MEL : Monochromatic excimer light
22. SNP : Single nucleotide polymorphisms

ABSTRACT

Background: Alopecia areata (AA) is a common form of non-scarring hair loss of scalp and/or body. Genetic predisposition, autoimmunity, and environmental factors play a major role in the etiopathogenesis of AA. Patchy AA is the most common form. Alopecia areata (AA) is considered as a T-cell infiltrated autoimmune disorder. The 308-nm excimer laser is thought to be capable of inducing T-cell apoptosis in vitro, suggesting that the 308-nm excimer lamp (not laser) might be effective for the treatment of AA. Several topical corticosteroids with varying levels of efficacy have been used to treat alopecia areata.

Objectives: Objective of this study is to compare the efficacy of 308-nm excimer lamp *vs*. topical micronized fluticasone propionate 0.05% cream in the treatment of alopecia areata.

Materials and method: Twenty five patients with two or more comparable patches of alopecia areata (AA) were recruited into the study. One patch was treated with 308nm excimer lamp twice weekly (test patch) and other patch with topical micronized fluticasone propionate 0.05% cream twice daily (control patch). The total duration of treatment was for three months and a monthly follow up for three months. Baseline clinical images and dermoscopic images were taken. After the end of therapy, clinical and dermoscopic images were taken during the follow up period of monthy three months to assess hair regrowth. The 2 primary efficacy parameters assessed were: Increase from baseline hair count at 12 weeks and hair regrowth score on six point scale at 12 weeks and during the follow up. Two blinded investigators evaluated response on computer screen using dermoscopic images.

Results: (1) Hair counts – The mean increase in hair count at week 12 was significantly greater for the study group compared to the control group. (2) Hair

regrowth score – In the study group, hair regrowth was started at 4th session onwards with score of 3-4 and whereas in control group hair regrowth was started at 14th session onwards with score of 1-3.

Conclusion: The results of this study did not establish "topical fluticasone cream" as a unique therapeutic modality for AA. The results with "excimer therapy" indicated that this therapy induces effective hair regrowth within short duration without any serious side effect for treating AA. However, the total number and frequency of sessions and long-term sustainability of response of excimer therapy need to be evaluated within a larger population.

Key Word : AA, Alopecia areata.

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INTRODUCTION

Alopecia areata is a common, non-scarring, autoimmune disorder affecting any hair-bearing area. It is often psychologically devastating. This disorder occurs equally in both the sexes and in all age groups. The peak incidence is between 20 and 50 years of age. It is characterized by the sudden appearance of circumscribed areas of hair loss on the scalp or other parts of the body.[1] Alopecia areata is mainly a cosmetic concern, causing more emotional problems, especially in children and women.

Genetic predisposition, autoimmunity and environmental factors play a major role in the etiopathogenesis of alopecia areata.[2] About 20% of people with alopecia areata have a family history of the disease, indicating a genetic predisposition. It is believed that hair follicle is an immune-privileged site.[2] The hair follicle is infiltrated by T lymphocytes.[3]Alopecia areata is considered as an autoimmune disease. The association with other autoimmune diseases like autoimmune thyroiditis, pernicious anemia, diabetes mellitus, vitiligo, and psoriasis is the reason to consider alopecia areata as an autoimmune disease.[2]

Peribulbar and intrabulbar lymphocytic inflammatory infiltrate resembling "swarm of bees" is characteristic on histopathology. There is an increase in number of catagen and telogen follicles.[2] This peribulbar inflammation adversely affects hair follicle activity, resulting in thin dystrophic hair with miniaturization. Thus alopecia areata is considered as hair follicle-specific autoimmune disease, triggered by environmental factor in genetically susceptible individuals.[2]

The lesions are usually round or oval flat patches of alopecia with normal skin colour and texture involving the scalp or any other hairy region of the body.[1] The disease can present as a single, well demarcated patch of hair loss, multiple patches, or extensive hair loss of scalp hair alopecia totalis (AT) or loss of entire scalp and body hair alopecia universalis (AU).[4]

Many therapeutic modalities have been used to treat alopecia areata with variable efficacy and safety profiles which are outlined below in the table 1.

Table 1: Treatment options in alopecia areata

TOPICAL	Corticosteroids
	Minoxidil
	Anthralin
	Immunotherapy
	Phototherapy
	Prostaglandin analouges
SYSTEMIC	Corticosteroids
	Sulfasalazine
	Psoralen plus ultraviolet A (PUVA)
MISCELLANEOUS	Cyclosporine A
	Methotrexate
	Azathioprine
	Capsaicin
	Topical bexarotene 1% gel
	Camouflage
	Calcineurin inhibitors
	Biologicals
	Narrowband ultraviolet B (NBUVB)

A number of treatments can induce hair regrowth in alopecia areata but do not change the course of the disease. Treatment is generally effective in localized lesions than in extensive disease.

The 308-nm excimer lamp is thought to be capable of inducing T-cell apoptosis in vitro, suggesting that the lamp might be effective for the treatment of alopecia areata. This condition has been successfully treated using psoralen plus ultraviolent A (PUVA) therapy. The disadvantage of PUVA is that large areas of normal skin are exposed to UV radiation along with alopecia lesions. To avoid unnecessary irradiation to uninvolved skin, PUVA therapy is not applicable to single or a few alopecia areata lesions.[5]

Monochromatic excimer light, which acts specifically on T lymphocytes, keratinocytes and dendritic cells and provokes apoptosis, has the advantage of a lower cost compared with the laser system.[5] Excimer light are capable of delivering large fluences of narrowband ultraviolent (UV) B selectively to cutaneous lesions within a reasonable time.[6] The 308-nm excimer lamp is smaller and less expensive and could allow targeted phototherapy to become more accessible.[7]

In this study, excimer lamp will be used for the treatment of alopecia areata on test site due to its ability to deliver high doses of ultraviolent (UV) irradiation to limited skin sites and topical fluticasone propionate 0.05% cream on control sites.

OBJECTIVE OF THE STUDY

To determine the efficacy of 308nm excimer lamp vs topical fluticasone cream in the treatment of alopecia areata.

REVIEW OF LITERATURE

ALOPECIA AREATA

Definition :

Alopecia Areata is an autoimmune disease, characterized by non-scarring hair loss on the scalp or any hair bearing surface.[1] The various synonyms for this condition are alopecia circumscriptum, pelade, area celsi.

Historical aspects :

It was first described about 2000 years ago by Celsus (AD1437) and the designation alopecia areata is by sauvages.[8] Hebra demonstrated the incorrectness of the hypothesis of fungal etiology as proposed by Willan and Gruby (1843). Later, Von Baresprung proposed the neurotrophic theory, and Jacquet elaborated the dystrophic theory, considering the disease to be caused by infectious focuses, particularly dental, a hypothesis that at present day has been totally discarded.[9]

Epidemiology :

Alopecia Areata is a common disease with a reported lifetime risk of 1.7%. Both men and women are equally affected with same prevalence in all ethnic groups.[1] Alopecia areata can occur at any age, but the peak incidence appears to be between 20 and 25 years of age.[10] It is reported to occur before the age of 16 years in 11% to 23.9% of the affected population. Traditionally, AA has been classified as an acquired disorder. However, it is rarely reported in infancy and even less so in the neonatal period.[11]

Patients usually present with several episodes of hair loss and hair re-growth during their lifetime. The course is irregular and unpredictable. Recovery from hair

loss may be complete, partial, or none. But the incidence of the severe chronic form of the condition is 7% to 10% in affected people.[12] Indicators of a poor prognosis are atopy, association with other immune diseases, family history, young age of onset, nail changes, extensive, and ophiasis types.[2]

Aetiology :

The etiology of AA is still an enigma. Many hypotheses have been proposed. Epidemics of AA reported from orphanages and schools pointed towards infectious etiology.[2] Many factors have been described in its pathogenesis like, genetic, psychogenic, family history, the atopic state, non-specific immune and organ specific autoimmune reaction, possible emotional stress, infectious agents and neurological factors.[11] Alopecia areata occuring in monozygotic twins and a strong family history for many generations in families of AA individuals shows that AA can be inherited. In AA, 4-28% had one affeted family member, and a polygenic inheritance was suggested.[2]

Immunological alterations :

Evidence of the non-genetic etiology of AA is limited. Several environmental factors such as infections, stress factors, toxins, and diet have been incriminated but not confirmed. The genetic basis of the disease is polygenic and is probably modified by environmental factors.[10] Alopecia areata has been strongly associated with major histocompatibility complex genes on chromosome-6, especially the class II alleles (HLA-DQB1*0301 and HLA-DRB1*1104). On chromosomes 10, 16 and 18 susceptibile loci have been noted. Recently, genome wide association studies (GWAS) have identified specific genetic markers for AA, which may increase risk for

AA.[2,13] Petukhova et al. surveyed the entire genome and identified 139 single nucleotide polymorphisms (SNPs) for AA, clustered in 8 regions of the genome.[14] Genome wide association studies have found key genes in AA related to T-cells (IL2/IL21, IL2RA, CTLA4, IKZF4, HLA) and hair follicle (NK-activating ligands-ULBP3, ULBP6, STX17, PRDX5).[15] All these are suggestive of genetic predisposition in the development of AA.

The association of AA with autoimmune diseases was first suggested by Rothman.[13] There are reported associations of AA with pernicious anemia, diabetes, lupus erythematosus, myasthenia gravis, rheumatoid arthritis, polymyalgia rheumatica, ulcerative colitis, lichen planus, and candida endocrinopathy syndrome.[12] The circulating organ and non-organ-specific autoantibodies with increased frequency are seen in patients with AA compared with control subjects. In peripheral blood of AA patients, hair follicle specific antibodies are increased, especially to keratin 16 and trichohyalin. It is believed that hair follicle is an immune- privileged site. In healthy hair follicle epithelium, major histocompatibility complex (MHC) class I and II molecules are not expressed and transforming growth factor beta (TGF- β), insulin like growth factor 1 (IGF-1), and alpha melanocyte stimulating harmone (α-MSH) are more expressed. This immune privilege is collapsed in AA by the presence of increased MHC I and II complexes, decreased immunosuppressive molecules, and higher expression of adhesion molecules, intracellular adhesion molecule 2 and endothelial cell leukocyte adhesion molecule 1 (ICAM-2 and ELAM-1) in the perivascular and peribulbar hair follicular epithelium, leading to perifollicular inflammation. This peribulbar inflammation adversely affects hair follicle activity, resulting in thin dystrophic hair with miniaturization. Thus, AA is considered as hair

follicle-specific autoimmune disease, triggered by environmental factors in genetically susceptible individuals.[1]

Pathogenesis of alopecia areata :

Putatively, hair follicles are immune privileged sites. Alopecia areata develops in susceptible individuals as a result of a failure in hair follicle immunoprotection. In the anagen phase of hair follicle growth, no Langerhan's cells can be detected and in two-thirds of hair follicles proximal to the hair bulb. Follicles are also devoid of Class Ia MHC antigens in the proximal hair follicle epithelium. Moreover, NK cells, CD4+ T-cells and CD8+ T-cells are not observed in the lower portion of the proximal hair follicle and hair bulb. In addition, immunosuppressive cytokines such as transforming growth factor- beta 1 (TGF-β1) and alpha melanocyte-stimulating hormone (α-MSH) are generated locally, which may further hinder MHC class I expression in anagen-stage hair follicles. Loss of immune privilege may be the primary initiating event for AA & may not affect hair follicle growth directly.[16]

The development of hair loss involves aberrant modulation of the hair growth cycle, resulting in dystrophic anagen hair follicles and/or increased frequency of telogen state follicles.

There are several possible presentations of AA. First, the anagen phase of a hair follicle can become inflamed and maintained in a dystrophic anagen state, unable to produce hair fiber of significant size or integrity.[16] When there is a greater intensity of inflammation, the hair follicles may be forced into a telogen phase and may then cycle through multiple anagen-telogen phases of brief duration. Correspondingly, inflammatory cell infiltration occurs in early anagen follicles without migration to draining lymph nodes as follicles capitulate and return to telogen. Finally, when AA is

chronic, the hair follicles tend to persist in a prolonged telogen phase without an apparent attempt to return to the anagen phase.[16]

Recent studies have indicated that AA is an inflammation-driven disease and is likely an autoimmune disorder. The presence of inflammatory lymphocytes around and within affected hair follicles and the ability to promote hair regrowth with the use of immunosuppressive agents is consistent with an autoimmune hypothesis.[17] The infiltration of antigen presenting cells (APCs) such as macrophages and Langerhans cells both around and within the dystrophic hair follicles has also been observed. The presence of hair follicle specific IgG autoantibodies in the peripheral blood of AA patients also further reinforces the hypothesis that the development of AA could be autoimmune related.[17]

Classification & clinical features :

Alopecia can be broadly classified either based on Ikeda's types or based on the pattern of hairloss which are listed in the table 2.[13]

Table 2: Classification of alopecia areata

Ikeda classified AA based on the associated conditions and on the course of the disease :	
Atopic type	It begins early in life and mostly (30-75%) progresses to alopecia totalis.
Autoimmune type	It is seen in middle-aged groups and is associated with autoimmune diseases, and progresses to alopecia totalis in 10-50%.
Prehypertensive type	It is seen in young adults whose parents are hypertensive and progress rapidly to alopecia totalis in 40% of cases.
Common type	It affects adults aged 20-40 years and alopecia totalis develops in 5-15% of cases.
Based on the pattern of hair loss, alopecia areata is classified into :	
Reticular	Small distinct patches may merge and form larger patches.
Ophiasis	It is a band-like AA along the posterior occipital and temporal margins.
Sisaipho	Also called as ophiasis inversus, presents with alopecia involving the frontal, temporal, and parietal scalp but spares hair along the scalp periphery, mimicking androgenetic alopecia.
Based on the extent of hair loss :	
Patchy alopecia areata	Single or multiple circumscribed patches
Alopecia totalis	Alopecia affecting entire scalp hair.
Alopecia universalis	Alopecia affecting all hair bearing areas.
New variants:	
Acute and diffuse total alopecia	It is characterized by female preponderance, generalized hair thinning, rapid progression, tissue eosinophilia, extensive involvement, brief clinical course, and favorable prognosis.
Unusual patterns:	
Perinaevoid and linear alopecia areata	Alopecia patches around the nevi, and unusual presentations may occur in linear distribution.

Alopecia areata is most often asymptomatic. Occasionally patients may feel mild pruritus or burning sensation. It can affect any hair bearing area, but scalp is more commonly affected. Alopecia areata usually presents as well defined patches of hair loss on the scalp but any hair-bearing skin can be involved. Typically, surface of the patches is smooth and the colour of skin is normal without any secondary changes like scaling and follicular changes. Rarely, it can be erythematous. Characteristic 'exclamatory mark hairs' are seen either within or at the border of the patches. These are short hairs with proximal tapering, close to scalp and distal thickening and widening. A positive hair pull test at the periphery of a patch usually means that the disease is active. The diagnosis is mostly clinical. Dermoscopy is useful in doubtful cases.

Dermoscopy :

It is an easy & useful technique to observe hair loss. Dry dermoscopy, also called trichoscopy, is ideal because it has the blocking filter against light reflection from the skin surface and it can be done directly without application of the gel. Yellow dots, black dots, broken hairs, tapering hair (exclamation marks), and short vellus hairs are characteristic dermoscopic feature shown in figure 1. Inui *et al*. described coudability hairs on trichoscopy and suggested that they are useful markers for disease activity in AA. By the presence of black dots, broken hair, activity of the disease is suggested. Black dots and yellow dots are proportional to severity of AA, and tapering hair does not have any correlation with severity. Yellow dots are also seen in androgenetic alopecia, but they are few in number, whereas in AA, they are abundant. Single feature on dermoscopy may not be diagnostic of AA, but a combination of features are helpful in detecting difficult cases like AA incognito.[2]

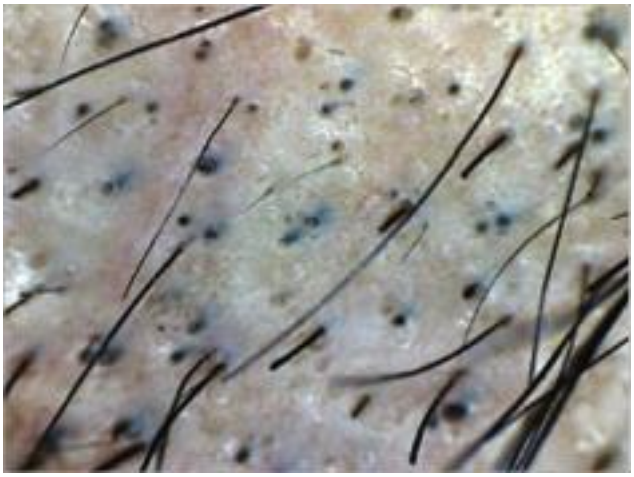


Figure 1 Dermoscopy picture of Alopecia areata, showing black dots, yellow dots, broken hair & tapering hair.

Histopathology :

The histopathologic findings in AA vary with the duration of disease. It is ideal to perform two 4 mm punch biopsies including subcutaneous fat. The advancing border of hair loss is the best place to biopsy. This helps to view the hair follicles at different levels in dermis to quantify the hair follicle density, follicle diameter, and to assess the proportion of hair follicles in various stages.

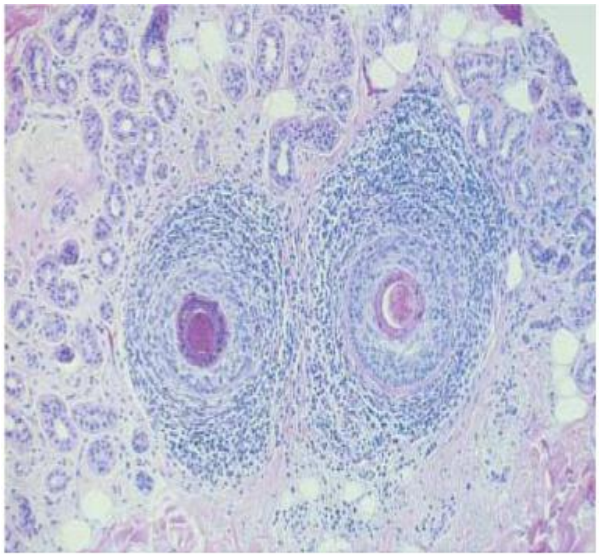


Figure 2 'swarm of bees' appearance of the inflammatory infiltrate around terminal hair follicles in AA (H & E STAIN, 10X)

The characteristic histopathplogical feature in acute cases is peribulbar & intrabulbar lymphocytic infiltrate around anagen follicles, resembling 'swarm of bees' shown in figure 2. In subacute lesions, a high proportion of catagen/telogen hair follicles are seen. In chronic cases, follicular miniaturization with variable inflammatory infiltrate is seen in pappilary dermis. The lymphocytes are mainly present around the hair matrix and dermal papilla and spare the bulge area, causing follicular edema, cellular necrosis, microvesiculation, and pigment incontinence. The terminal to vellus hair ratio is decreased to 1:1 in contrast to 7:1 unaffected area.[2,13]

Differential diagnosis :

The diagnosis of alopecia areata is usually straightforward although the following may cause diagnostic difficulties[13]:

Scarring alopecia :

- Cicatricial alopecia,
- Secondary syphilis,
- Tinea capitis.

Non scarring alopecia :

- Trichotillomania,
- Androgenetic alopecia,
- Telogen effluvium,
- Congenital triangular alopecia,
- Pressure alopecia,
- Traction alopecia and
- Systemic lupus erythematosus.

Role of genetics in alopecia areata :

The genetics of an individual can play an important role in the development of AA which can also be inherited based on observations on monozygotic twins. Some patients with AA have a strong family history that spans many generations, and this suggests that AA can be inherited. Human leukocyte antigen (HLA) class II antigens are aberrantly highly expressed on AA affected hair follicles. The DQB1*03 and DRB1*1104, are specific alleles which have been reported as markers for susceptibility to AA. Linkage analysis with the AA mouse model revealed that AA is a complex polygenic trait. A genome-wide study was completed on extended human families with multiple AA patients. Intervals on human chromosomes 6, 10, 16, and 18 were identified as potential AA susceptibility loci. There was at least one significant genetic determinant of AA found at 6q.23.3 outside of the HLA gene cluster. Large scale, genome-wide screens using the AA registry and DNA bank are nearing completion and should provide significant new information on the potential gene activity in AA development beyond the HLA region.[18]

Environmental impact on alopecia areata :

Environmental factors may also contribute to AA development and likely determine the actual onset, hair loss pattern, and severity of the disease. However, the exact environmental stimuli required for AA expression are yet to be determined. Hormonal fluctuation, infectious agents, and vaccinations have all been cited as possible triggers for AA. In the mouse model, dietary soy oil increases resistance to AA development, suggesting that diet might also play a role in AA susceptibility. In a mouse model study, the development of AA was strongly associated with higher central and peripheral hypothalamic-pituitary-adrenal (HPA) tone indicating hormonal changes also play a role.[18]

Hypothesis for alopecia areata development :

Currently, AA development hypotheses focus on hair follicle immune privilege collapse or the inappropriate presentation of antigens to the immune system during normal hair follicle cycle. Anagen stage hair follicles retain immune privilege and a breach in immune privilege leads to exposure of unique hair follicle antigens which may result in targeting by the skin immune system. An alternative hypothesis is based on the knowledge that hair follicle immunoprotection is transient and limited to the anagen growth cycle stage.

Inappropriate excitation of antigen presenting cells during disordered catagen and migration of cells to draining lymph nodes may lead to hair follicle antigen specific lymphocyte activation, migration, and infiltration of anagen stage hair follicles.[18]

A recently proposed hypothesis is the faulty upregulation of an immune signal that mistakes the hair follicle for an infected or dying cell, and therefore launches the release of cytotoxic T cells that attack the end organ. A key source for fuelling those

particular killer T cells in an autoimmune response is IL-15, and therefore, therapies could be aimed at blocking the IL-15 signal that sustains those killer T cells.[13]

Macrophage migration inhibitory factor (MIF) seems to have an essential role in the etiopathogenesis of AA. There is also a positive correlation between MIF levels and clinical severity and disease duration. So, it is considered to be a promising target in the therapy of autoimmune diseases and as a future predictor of alopecia activity. Anti-MIF therapy might be added as one of the new biological treatments for AA.[13]

Course and prognosis :

The progress of AA is that it is unpredictable which means that one cannot reliably predict which patients will have limited disease with spontaneous resolution and which will have recurrent disease or chronic, severe disease. Regrowth occurs spontaneously in many patients. Most of them will have more than one episode. Fifty to eighty percent of patchy AA patients may regrow hair in one year. Few of them may persist for longer time, and some may never recover hair. Some of the clinical features suggest poor prognosis.

- Younger age of onset
- Family history of AA or atopy
- Severe disease - Pattern (ophiasis, alopecia totalis, alopecia universalis)
- Duration >1 year
- Nail disease
- Associated autoimmune disease

In children, the disease may have a tendency towards worsening with time, even if the initial presentation was mild. Five to ten percent may progress to AT/AU. The chance of full recovery is less than 10% in AT/AU.[2,13]

Associated abnormalities :

Ten to twenty two percent of the cases are associated with AA, twice the prevalence in general population. Eight to twenty eight percent of cases are associated with autoimmune thyroiditis. The other associated conditions are vitiligo, psoriasis, diabetes mellitus, Down's syndrome, Addison's disease, autosomal recessive autoimmune polyglandular syndrome, systemic lupus erythematosus, celiac disease, ulcerative colitis, and multiple sclerosis.

These are less common and are more likely to be associated with AT/AU. Sharma *et al*. reported that presence of vitiligo in family members was a definite risk factor for developing severe forms of alopecia. Patients presenting with AA in childhood (<10 yrs of age) are most likely to have atopic dermatitis or systemic lupus erythematosus, patients in the second decade have high risk for psoriasis or rheumatoid arthritis and patients presenting with AA in the old age (>60 years) are more likely to have thyroid disease.[2]

Seven to sixty six percent nail involvement may be observed in AA. Nail pitting is the most common nail abnormality observed is nail pitting. Trachyonychia, Beau lines, onychorhexis, thinning or thickening, onychomadesis, koilonychias, punctuate or transverse leukonychia, and red spotted lunulae are other abnormalities. Nails can be affected before, concurrent with, or after the resolution of hair loss. Several studies have suggested that nail abnormalities are associated with more extensive hair loss.[18]

There may be a high psychiatric morbidity in AA, especially anxiety and mood disturbance. In one report, ophthalmologic findings such as asymptomatic lens opacities and fundus changes occurred in 51% and 41% of AA patients respectively.[18]

Treatment:

Treatment modalities are usually tailored as per the extent of hair loss of hair loss and patient's age.[1] Spontaneous remissions can occur in up to 80% of limited alopecia areata within one year. The focus of treatment is mainly towards curtailing the disease activity.[2] The high rate of spontaneous remission makes it difficult to assess the efficacy particularly in mild forms of the disease.[3]

Topical treatment options:

Topical corticosteroids: Several topical corticosteroids with varying levels of efficacy have been used to treat alopecia areata. These include fluocinolone acetonide cream, fluocinolone scalp gel, betamethasone valarate lotion, clobetasol propionate ointment, dexamethasone and halcinomide cream. They are good option in children because of their painless application and wide safety margin. Topical corticosteroids are ineffective in alopecia totalis/universalis. Folliculitis is a common side effect of corticosteroid, appearing in a few weeks of the treatment. Telangiectasia and local atrophy have also been reported. They can be applied alternate day or 5days a week to prevent atrophy. Treatment must be continued for a minimum of 3 months before regrowth can be expected.[1] Application under occlusion increases the potency of topical corticosteroids.[2]

Intralesional corticosteroids: These are the first-line treatment in localized conditions involving <50% of the scalp. Hydrocortisone acetate (25mg/ml) and triamcinolone acetonide (5-10mg/ml) are commonly used.[1] Triamcinolone acetonide is preffered. Various concentrations (2.5-10mg/ml) are used, but 10mg/ml is preferred for scalp and 2.5mg/ml for eye brows and face.[2] Regrowth usually is seen within 4-6 weeks in responsive patients. Treatment are repeated every 3-6 weeks. Repeated injections at the same site or use of same concentrations should be avoided as this may lead to skin atrophy.[1]

***Minoxidil*:** Minoxidil is effective in the treatment of alopecia areata. It is known to stimulate DNA synthesis in the hair follicles and has direct action on the proliferation and differention of the keratinocytes.[1] In one clinical study, hair regrowth was achieved in 38% and 81% of patients treated with 1% and 5% topical minoxidil, respectively.[4] Thus 5% minoxidil solution is usually recommended as a treatment option in alopecia areata. Minoxidil 5% solution or foam is frequently used with other therapeutic agents as an adjuvant therapy.[4] It is generally well tolerated, but unwanted facial hair was noticed in 3% women. Pruritus or dermatitis are other rare adverse effects.[2]

***Anthralin*:** It is an irritant, and its mechanism of action in alopecia areata is unknown. It is effective because of its immunosuppressive and anti-inflammatory properties by generating free radicles.[2] It is used as 0.5-1% cream with short contact therapy for 20-30 minutes after which the scalp should be washed with shampoos in order to avoid excessive irritant effects. The applications are made initially every other day and later on daily. Adverse effects include pruritus, erythema, scailing, staining of treated skin and fabrics, folliculitis, and regional lymphadenopathy.[1]

***Topical immunotherapy*:** Topical immunotherapy is the best treatment for severe and refractory cases of alopecia areata. It is induction and periodic elicitation of allergic contact dermatitis by applying a potent contact allergen.[1] Topical sensitizers that have been used in the treatment of alopecia areata include diphenylcyclopropenone(DPCP), squaric acid dibutylester (SADBE), and dinitrochlorobenzene. Dinitrochlorobenzene is no longer used because it was shown to be mutagenic in the Ames test. Diphenylcyclopropenone is the topical sensitizer of choice. Squaric acid dibutylester is expensive and not stable in acetone. Diphenylcyclopropenone is light sensitive and should be protected from light. The diphenylcyclopropenone concentration is increased gradually every week until mild dermatitis is observed. The solution should be in contact with the scalp for 48 hours. The scalp should be protected from the sun during this time. Diphenylcyclopropenone is applied on a weekly basis by a trained nurse. If there is no response after 6 months of treatment, diphenylcyclopropenone can be discontinued. Squaric acid dibutylester may be tried in poor responders to diphenylcyclopropenone or in those who do not develop a sensitization to 2% diphenylcyclopropenone. Squaric acid dibutylester is applied once or twice per week. The adverse effects to topical sensitizers include cervical lymphadenopathy, a severe eczematous reaction, urticaria, and postinflammatory pigment changes.[4]

***Prostaglandin analogues*:** Latanoprost and bimatoprost are prostaglandin analogues, which are used in open angle glaucoma caused hypertrichosis of eyelashes and hair on the malar area as an adverse effect. Because of this effect, these were tried in eyelash alopecia areata.[2] In a nonrandomized, controlled study of latanoprost (a prostaglandin F2α analog) eye drops in patients with alopecia universalis, acceptable results (total and moderate hair regrowth) were achieved in 45% of patients. In another

retrospective trial, 0.03% bimatoprost eye drops were used once a day for one year. Complete regrowth of the eyelashes was noted in 24.3% of patients and moderate growth in 18.9% of treated subjects. Relapses were observed in 17.5% of the patients, mainly in the slight response group.[4]

***Topical calcinuerin inhibitors*:** Topical calcinuerin inhibitors, tacrolimus, and pimecrolimus inhibit transcription following T-cell activation of several cytokines. They were tried in AA and were found to be ineffective.[2]

Systemic treatment options :

***Systemic corticosteroids*:** Systemic corticosteroids have been used daily, weekly and monthly pulses with good improvement in patchy alopecia areata and less favorable outcome in ophiasis, alopecia totalis /universalis.[2] The suggested dosages are 0.5-1mg/kg/day for adults and 0.1-1mg/kg/day for children. Treatment course ranges from 1-6 months.[1] Long-term daily treatment with oral corticosteroids will produce regrowth of hair in some patients. Pulsed administration employs a high dose oral corticosteroid on two consecutive days every week with a gap of 5 days between the two pulses. This modality of treatment is known as oral minipulse therapy (OMP) and it has been tried in many skin diseases in addition to alopecia areata.[1] Alopecia totalis and alopecia universalis are far less responsive to this therapy than patchy alopecia areata. The use of systemic corticosteroids is limited by their side effects (hyperglycemia, weight gain, hypertension, adrenal suppression, dysmenorrhea, immunosuppression, and acneiform eruption) and the high relapse rate (14%–100%).[4]

***Sulfasalazine*:** It is a combination of sulfapyridine and 5-aminosalicylic acid linked by a diazo bond. Sulfasalazine has both immunomodulatory and immunosuppressive actions. It causes suppression of T cell proliferation and reducing the synthesis of cytokines, including interleukin (IL) 6, 1, and 12, tumor necrosis factor alpha and antibody production.[4] Treatment is started at a lower dose, usually in the range of 500 mg twice daily and then the dose is gradually increased to 1g three times a day adverse effects include gastrointestinal distress, liver toxicity and haemotological side effects.[1]

***Azathioprine*:** A thiopurine analogue immunosuppressive drug, has been tried in alopecia areata.[1] It inhibits DNA synthesis and thus decreases proliferation of cells, especially T and B lymphocytes. Azathioprine also decreases the number of Langerhans cells and other antigen presenting cells.[4] In a recent pilot study of 20 patients treated with azathioprine 2 mg/kg/day as monotherapy, mean hair regrowth was 52.3% ± 38.4%.[2,4]

***Cyclosporine*:** This drug has proven effective in the treatment of alopecia areata because of its immunosuppressive and hypertrichotic properties.[1] The success rate with oral cyclosporine is 25%–76.6%. A recent study showed that a good response to oral cyclosporine can be predicted if the serum level of IL 18 is elevated and the level of soluble IL 2 receptor is low.[4] The use of oral cyclosporine is not favoured due to its adverse effects such as nephrotoxicity immune suppression, and hypertension and a high relapse rate.[1,4]

***Methotrexate*:** Methotrexate either alone or in combination with prednisolone has been used in the treatment of alopecia areata.[1] Adverse effects to methotrexate include persistent nausea, transient elevation of hepatic enzymes, and leucopenia.[4]

Bexarotene: In a randomized bilateral half-head study, hair regrowth of at least 50% on treated sites was noticed in only 26% of patients treated with 1% bexarotene gel. Mild irritation is a common side effect.[4,8] The mechanism of action is through immunomodulation and induction of T-cell apoptosis.[4]

Photo-and photochemotherapy:

Photochemothetherapy: There are several uncontrolled studies of psoralen plus ultraviolent A (PUVA) treatment for alopecia areata, using all types of PUVA (oral PUVA, topical PUVA, local or whole body UVA irradiation) have been used with success rate of up to 60-65%.[1] Psoralen plus ultraviolent A has been found to be effective in alopecia areata by decreasing the perifollicular inflammatory infiltrate.[2] Mild erythema, burning and increased risk for melanoma are some of the side effects observed with PUVA. To mitigate the side effects of systemic psoralens, PUVA-turban therapy is used in alopecia areata involving the scalp. In this form of photochemotherapy, very dilute solutions of 8-methoxy psoralen are applied on the scalp by utilizing a cotton towel as a turban. The patient's scalp is exposed to UVA after keeping the turban in contact with the scalp for about 20 minutes. Treatment sessions are performed every two or three times per week.[1,4] The efficacy of this form of PUVA therapy has been seen to be about 70%. The disadvantage of PUVA is that large areas of normal skin are exposed to UV irradiation along with alopecia lesions.

Excimer laser and excimer light: Excimer laser and excimer light are two more recent additions to the phototherapeutic armamentarium for many skin and hair disorders.[1] The 308-nm excimer lamp is capable of inducing T-cell apoptosis in vitro, suggesting that the lamp might be effective in the treatment of alopecia areata.[5]The

xenon chloride gas excimer offers a means of delivering larger fluences of narrowband UVB.[6]

Recently, units capable of delivering large fluences of narrowband UVB selectively to the cutaneous lesions within a reasonable time have been developed. The xenon chloride gas excimer offers a means for delivering larger fluences of narrowband UVB not far from 311-nm narrowband phototherapy.

Two systems emitting high-energy monochromatic excimer light (MEL) have been developed: (i) laser technology (ii) a new nonlaser MEL technology. Laser technology, already approved by the U.S. Food and Drug Administration for psoriasis treatment, and a new nonlaser MEL technology. This new MEL is 17 times more powerful compared with a Philips UVB TL- 01 source. The advantages over laser system are low operating cost and the fact that a large area can be treated quickly. The 308-nm excimer laser system produce a small spot size which requires multiple treatments of adjacent areas to cover the lesional skin.[6] Both devices deliver roughly the same wavelength, and different in terms of physical properties and cost.[7] The 308-nm excimer lamp induces more erythema than the 308-nm excimer laser for the same fluence, suggesting photobiological differences between the two devices. Although a bit slower than the laser, the cost/effectiveness ratio appears more favorable for the lamp.[7]

Excimer laser contains a mixure of a noble inert gas and a halogen, which form excited dimers only in the activated state. High-energy current is used to produce these dimers, which have a very short lifetime, and after their fast dissociation they release the excitation energy through ultraviolent photons. Excimer laser are pulsed

wave lasers, they deliver a high energy in a short time, thus rapidly breaking chemical bond. The pulse width of these lasers is so short that the temperature of surrounding material does not change, but remains intact. The laser can be delivered through a fiber optic cable, which makes it possible to selectively target different lesions on the body surface. Types of excimer laser include the 193-nm argon fluoride, the 248-nm krypton fluoride, the 351-nm xenon fluoride, and the 308-nm xenon chloride lasers are used. The major mechanism of its action is that it induces apoptosis of T cells, which are important in initiating inflammatory skin diseases.[19]

In a study by Ohtsuki *et al*,[5] that comprised of 3 female patients with single alopecia areata, lesions were treated with 308-nm excimer lamp. They successfully treated with approximately 10 sessions of treatment. Their study showed that 308-nm excimer lamp induces effective hair regrowth in patients with a single alopecia areata lesion. None of the patients reported hair loss during the follow up period of 4 weeks. Their therapy seemed to be more effective in treating single alopecia areata lesions compared with conventional narrow-band therapy.

In a study by Ohtsuki *et al*,[20] that comprised of 16 patients (4 male and 12 female) with localized or multiple alopecia areata were treated with 308-nm excimer lamp once every two weeks. The initial irradiation doses ranged from 150 to 200 mJ/cm^2 with dose increments of $50mJ/cm^2$ until the appearance of fine erythema. When erythema appeared dosage was fixed. Regrowth of hair was evaluated on a three-point scale: (Score 0, no effect; Score 1, hair regrowth involving less than 50% of scalp lesions; Score2, hair regrowth involving more than 50% of the scalp lesions). Hair regrowth was observed in 14 patients. Among them, 10 patients showed more than

50% hair regrowth, which suggest that 308-nm excimer lamp is a good therapeutic alternative without serious side effect for treating alopecia areata lesions compared with conventional narrow-band therapy.

In a study by Zakaria *et al*,[21] performed a comparative prospective intraindividual study to assess the effectiveness of the 308-nm XeCl laser that comprised of 9 patients with alopecia areata. Each lesion was treated twice a week for a maximum of 24 sessions. Initial fluencies were 50 mJ/cm^2. Then fluencies were increased from 50 mJ/cm^2 every two sessions. Cumulative doses ranged from 3.9 to 16.8J/cm^2. Five patients with alopecia areata partialis responded to treatment very well. Responders did not lose their hair over a follow-up period of 3 months. These results were obtained from moderate accumulated doses. On the other hand, no hair regrowth was observed in patients with alopecia areata totalis/universalis. Efficacy was blindly evaluated by two physicians on direct-light photos taken before sessions, and at the end of the sessions. Regrowth was graded on a 6-point scale (0 = no hair regrowth, 1 = hair regrowth 1%-24%, 2 = hair regrowth 25%-49%, 3 = hair regrowth 50%-74%, 4 = hair regrowth 75%-99%, and 5 = complete hair growth). Their study shows that 308-nm excimer laser induces effective hair growth in all patients with alopecia areata partialis (AAP). The side effects were limited to mild erythema and hyperpigmentation, and tolerance was excellent.

In a study by Aubin and colleagues,[6] that comprised of 8 patients of alopecia areata treated with 308-nm XeCl laser. The initial doses were based on multiples of a predetermined minimal erythema dose (MED), and subsequent doses were based on the response to the treatment. Treatments were scheduled weekly for a minimum of 5

weeks and a maximum of 10 weeks. Alopecia areata, was defined with a baseline score ranging from 0 (low) to 4 (high) according to the degree of induration (I), scaliness (S) and erythema (E). They observed 4 complete regrowths after a mean of 3.1 treatments. The mean number of MED was 9.1 per treatment. In 1 patient, one week after treatment, intense erythema and peeling occurred; after additional treatments for 6 weeks, complete regrowth was observed and was still present at the 6-month follow up visit.

In a study by Al-Mutari,[22] Patients with AA lesions persisting for more than 6 months were recruited. Patients were also required to discontinue all other topical/systemic therapy for at least 6 weeks before they were recruited into the study. Patients who were pregnant or who had a history of photosensitivity or keloid formation were excluded from recruitment. Every patient selected had at least one untreated AA patch that was used as a control site. Eighteen patients (4 children and 14 adults) with 42 recalcitrant patches (including one adult with alopecia totalis) that had not responded to different treatment modalities for AA were enrolled in study. There were 7 males and 11 females. Each lesion was treated twice a week for a maximum of 24 sessions (over 3 months). Initial fluences were 50 mJ/cm2 less than minimal erythema dose. Then fluences were increased by 50 mJ/cm2 every two sessions.

From review of the literature on 308-nm excimer lamp in the treatment of alopecia areata, it is evident that it is an effective therapeutic modality in the treatment of alopecia areata. The side effect profile of 308-nm excimer lamp is negligible and comparable to other treatment modalities for alopecia areata. The present study has been undertaken to evaluate the efficacy of 308nm excimer lamp vs topical fluticasone cream in the treatment of alopecia areata.

METHODOLOGY

SOURCE OF DATA:

A Hospital based Prospective study to determine the efficacy of 308nm excimer lamp vs topical fluticasone cream in the treatment of alopecia areata was conducted in the department of Dermatology, Venereology and Leprosy of BLDE University's Shri B.M. PATIL Medical College, Hospital and Research Center, Vijayapur, Karnataka. Twenty five patients with alopecia areata were recruited from the out patient section of the department. The study was conducted between November 2015 to July 2017.

METHOD OF COLLECTION OF DATA:

INCLUSION CRITERIA:

- Patients with multiple patches (atleast 2 comparable patches) of alopecia areata.
- Patients above 6 years of age.
- Duration of 6months

EXCLUSION CRITERIA:

- Patients aged less than 6 years.
- Patients on any kind of systemic/topical treatment for alopecia areata.
- History of photosensitivity
- Patients with alopecia totalis/universalis
- Patients with ophiasic pattern of alopecia areata.

Methods:

Equipments:

1. Phototherapy sources:

The 308-nm excimer lamp (Alma lasers) was used for the study. It is a monochromatic non-coherent light source with spot size 16 cm^2, which emits power density of 800 mW/cm^2. The light source is a xenon chloride lamp.

2. Dermoscope: In this study, a hand-held dermoscope (Dermlite™ DL3) was used. It is crafted from solid aluminium which integrates a 25 mm four-element lens with magnification of 10X and offers greatly reduced optical distortion with sharper image across the field of view. This dermoscope combines advantages of both PL and NPL. It has 28 high-powered LEDs, and a fully retractable and removable faceplate spacer design. The spacer comes with a glass faceplate with 10mm scale. It has a focal range in excess of ±4 mm. The device is camera compatible and is powered by rechargeable lithium-ion battery.

Methodology:

Detailed history with respect to the onset and duration of disease, any treatment (topical/systemic) received within the past 6 months, and pre-existing medical conditions were recorded from the patients in the (proforma enclosed).

Initial clinical examination of the patient was done by the investigator to determine the clinical type of alopecia areata, number of patches and other body site involvement. These findings were recorded at (first visit record).

In each patient 2 or more comparable patches of alopecia were selected for the study. These were allotted as ‘test’ and ‘control’ sites. In patients with more than one pair of comparable patches, several pairs of patches were taken as test and control

sites in the same patient. Test site was treated with 308-nm excimer lamp twice a week for a period of 12 weeks. Initial fluencies were given at 50mJ/cm^2. Fluencies was then increased by 50 mJ/cm^2 every session until the appearance of fine erythema (minimal erythema dose). The control site was treated with micronized fluticasone propionate (0.05%) cream twice daily for a period of 12 weeks. Baseline clinical images was taken for test and control patches for future comparison.

FOLLOW -UP:

Each patient was assessed for the treatment response at the interval of 4 weeks till 3months (total 3 follow up). During each follow-up two investigators assessed the treatment response with the help of trichoscope. Both test and control sites was assessed for hair count and density. Clinical images of test and control sites were taken during each follow up. Hair regrowth was graded on a 6-point scale as used by Zakaria *et al,*[11] as follows:

0 = no hair regrowth,

1 = hair regrowth (1%-24%),

2 = hair regrowth (25%-49%),

3 = hair regrowth (50%-74%),

4 = hair regrowth (75%-99%),

5 = complete hair growth

INVESTIGATIONS:

Following tests were done wherever necessary

- Complete blood count
- Urine examination

In case history suggestive of autoimmunity association or history of diabetes mellitus

- Thyroid profile
- Random blood sugar (RBS)

STATISTICAL ANALYSIS:

Clinico-epidemiological data collected from the patients were calculated with mean ± standard deviation (SD). Therapeutic response of the patients was represented diagrammatically. Chi-square test has been used to analyse the data.

ETHICAL CLEARANCE:

Institutional ethical committee clearance was taken for the study.

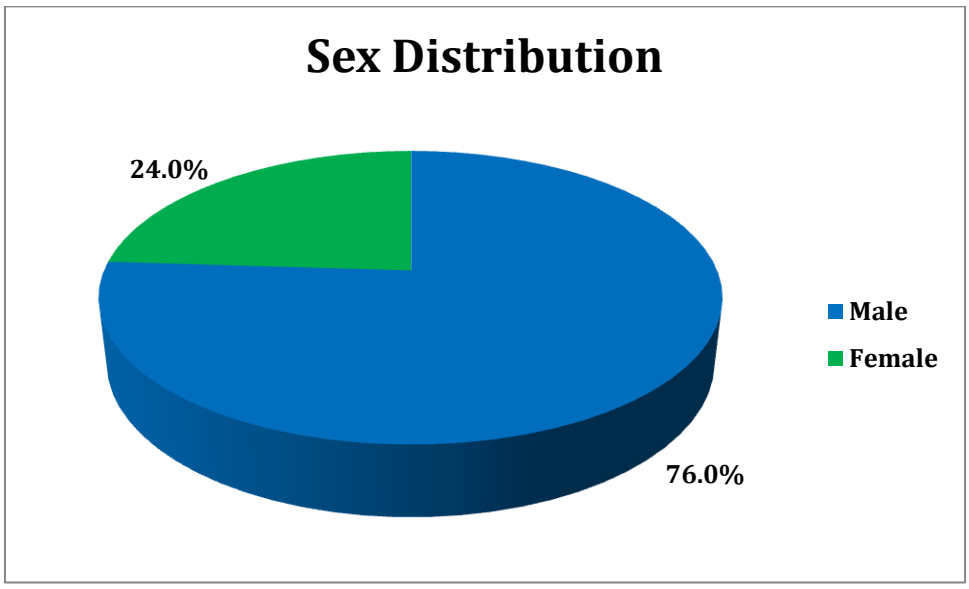
RESULTS

A hospital based prospective study was conducted from November 2015 to July 2017. Total 25 patients with alopecia areata were included in the study.

Gender distribution:

Among 25 patients, 19 were males (76%), and 6 were females (24%). There was statistically significant difference in the gender distribution of alopecia areata. Figure 3 presents the gender distribution of the patients with alopecia areata included in the study.

Figure 3: Distribution of cases according to Sex



Age distribution:

The age of the patients enrolled in the study ranged from 6 to 56 years. The mean age (± SD) of the study population was 22.8 (± 11.8) years. Figure 4 and table 3 represents the age distribution where as figure 5 and table 4 represents association of age by sex, of the patients with alopecia areata included in the study.

Table 3: Distribution of cases according to age

Age(years)	N	%
≤10	4	16
11-20	6	24
21-30	10	40
>30	5	20
Total	25	100

	Minimum	Maximum	Mean	SD
Age(years)	6	56	22.8	11.8

Figure 4: Distribution of cases according to age

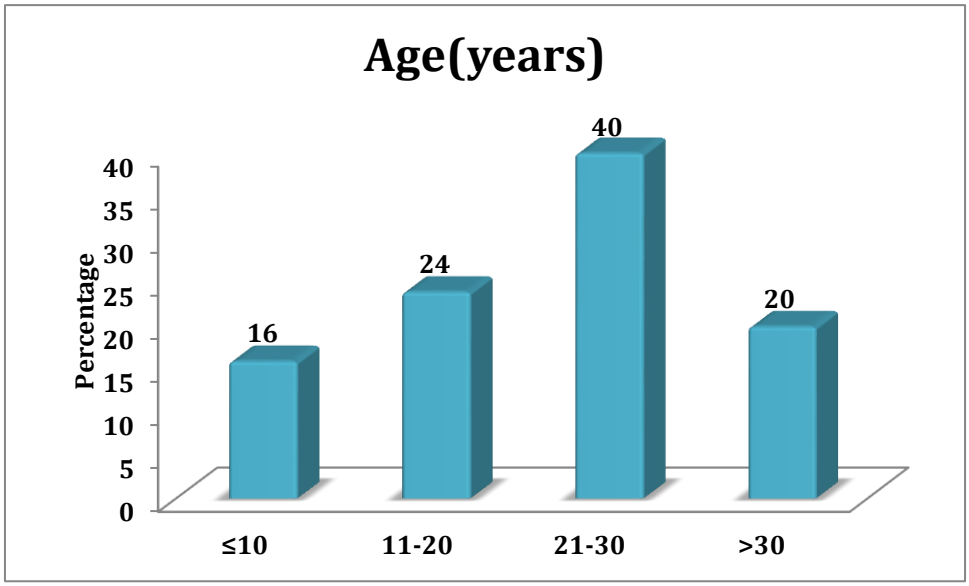
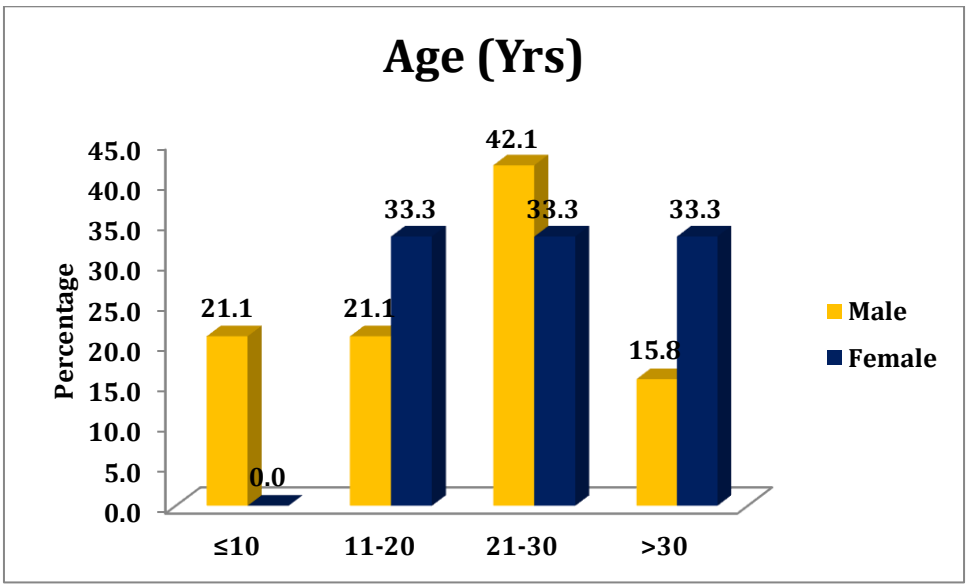


Table 4: Association of age by sex

Age(years)	Male		Female		p value
	N	%	N	%	
≤10	4	21.1	0	0.0	0.505
11-20	4	21.1	2	33.3	
21-30	8	42.1	2	33.3	
>30	3	15.8	2	33.3	
Total	19	100.0	6	100.0	

Figure 5: Association of age by sex



Location of alopecia areata:

Among 25 patients with alopecia areata, the most common location of was scalp with 22 (88%) patients and 3 (12%) patients had lesions over the scalp as well as over the beard area of the face. The percentage distribution of clinical types of alopecia areata has been presented in figure 6 and table 5.

Figure 6: Distribution of cases according to site of lesion

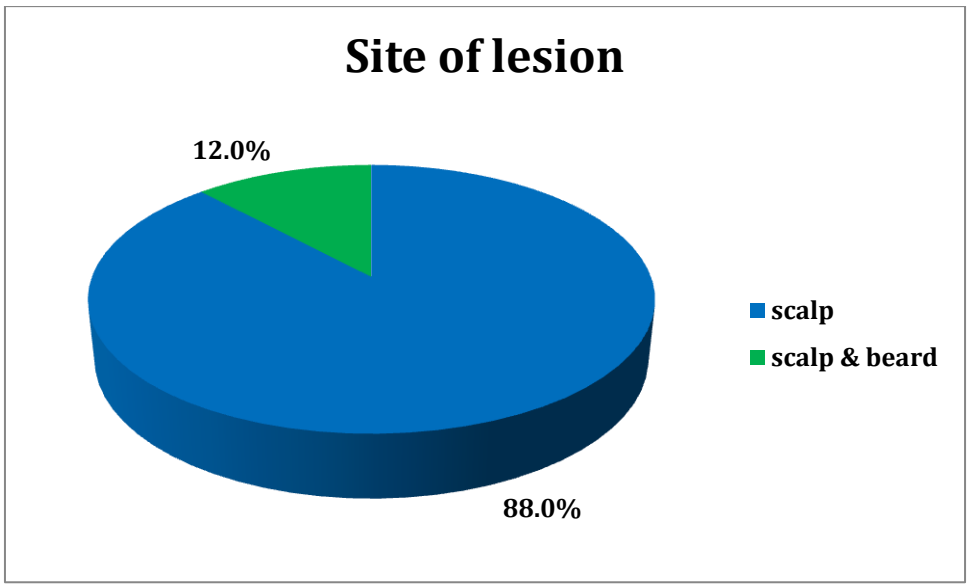


Table 5: Distribution of cases according to site of lesion

Site of lesion	N	%
scalp	22	88
scalp & beard	3	12
Total	25	100

No of lesions:

Most of the patients with AA had 2 patchy comparable lesions i.e,(test and control). Patients with 2 lesions were seen in 19 (76%) patients, 5 lesions were seen in 3 (12%) patients, and more than 5 lesions were seen in 2 (8%) patients. Figure 7 and table 6 represents the percentage distribution of no of lesions in patients with AA.

Figure 7: Distribution of cases according to no of lesions

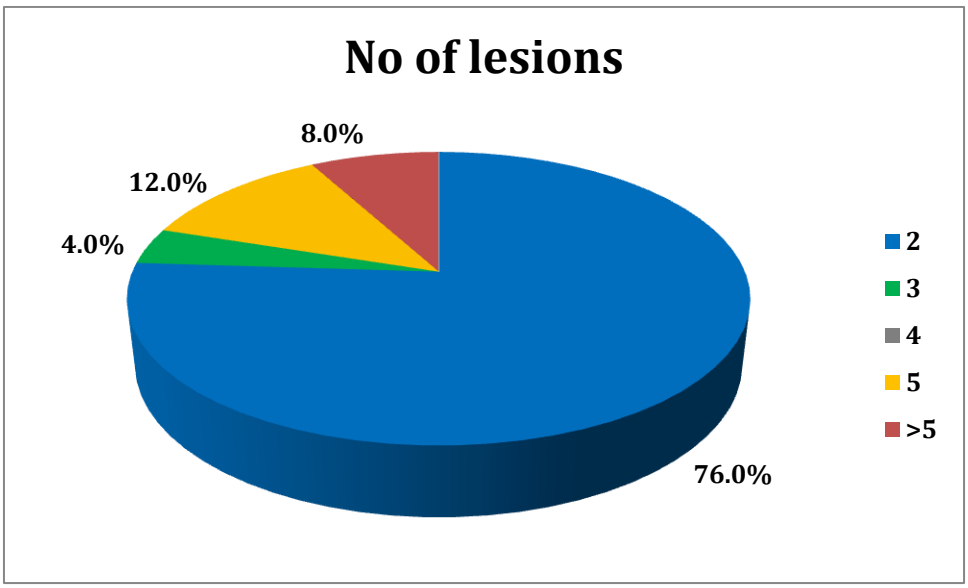


Table 6: Distribution of cases according to No of lesions

No of lesions	N	%
2	19	76
3	1	4
4	0	0
5	3	12
>5	2	8
Total	25	100

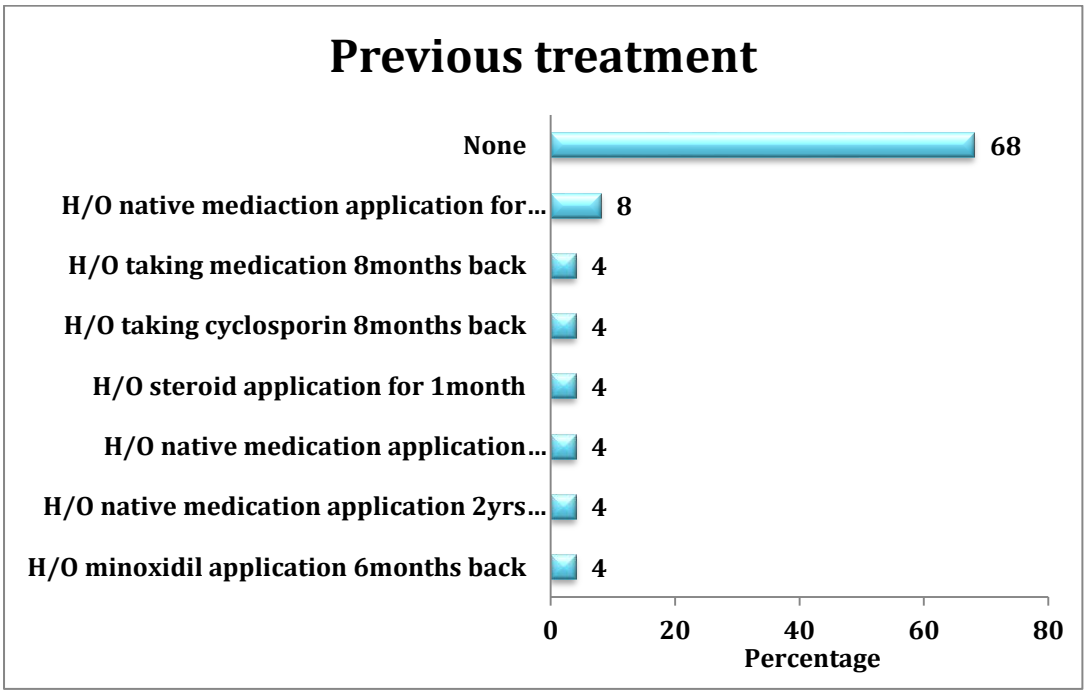
Previous treatment history:

History of receiving treatment in the past for AA was present in 8 (32%) patients and 17 (68%) patients had no previous history of treatment. Figure 8 and table 7 represents the distribution of the patients according to history of previous treatment of both study and control groups.

Table 7: Distribution of cases according to previous treatment received

Previous treatment received	N	%
H/O minoxidil application 6months back	1	4
H/O native medication application 2yrs back	1	4
H/O native medication application 6months back	1	4
H/O steroid application for 1month	1	4
H/O taking cyclosporin 8months back	1	4
H/O taking medication 8months back	1	4
H/O native mediaction application for 1week	2	8
None	17	68
Total	25	100

Figure 8 : Distribution of cases according to previous treatment received



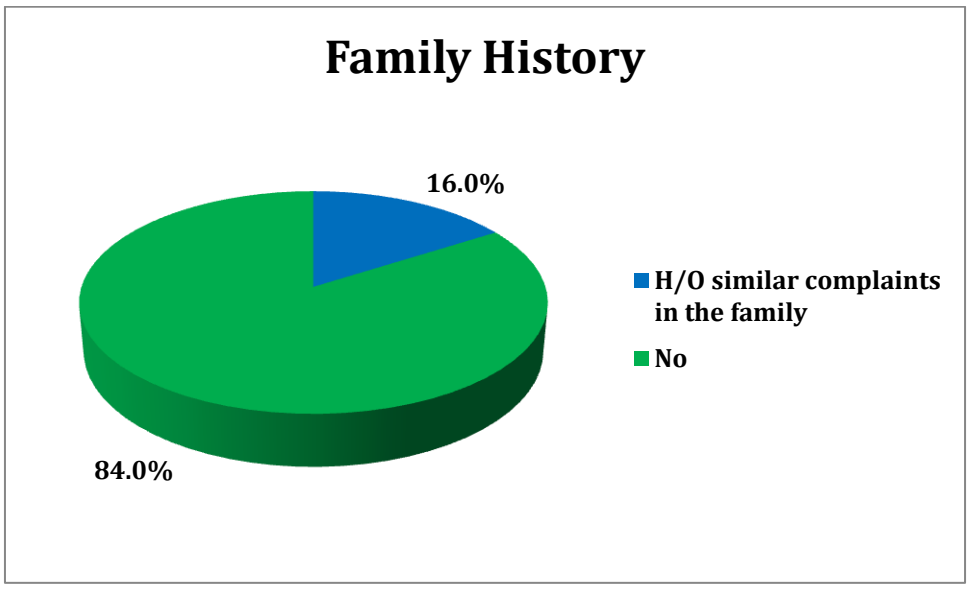
Family history:

Family history of AA was present in 4 (16%) patients and 21 (84%) patients had no family history. Figure 9 and table 8 represents the distribution of the patients according to family history of AA.

Table 8: Distribution of cases according to family history

Family History	N	%
H/O similar complaints in the family	4	16
No	21	84
Total	25	100

Figure 9 : Distribution of cases according to family history



Duration of lesion:

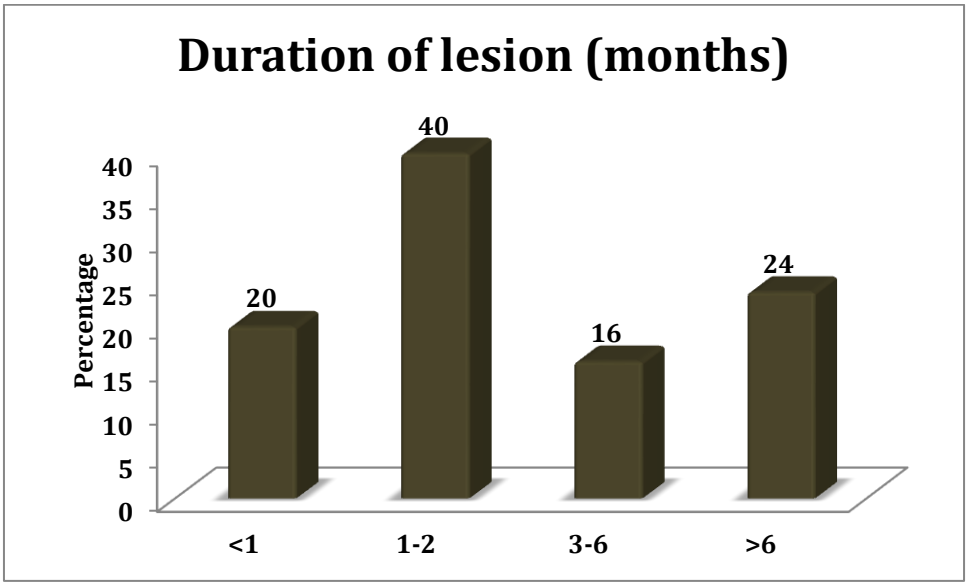
Among 25 patients about 10 (40%) had lesions for about 1-2 months, followed by 6 (24%) patients, who had lesions for >6 months. The mean duration (± SD) of AA was 10.9 (± 22.2) months. The percentage distribution of duration of lesions has been presented in figure 10 and table 9.

Table 9: Distribution of cases according to duration of lesion

Duration of lesion (months)	N	%
<1	5	20
1-2	10	40
3-6	4	16
>6	6	24
Total	25	100

	Minimum	Maximum	Mean	SD
Duration of lesion (months)	0.2	84	10.9	22.2

Figure 10: Distribution of cases according to duration of lesion



Nail changes:

Among 25 patients with AA all had nail changes with fine pits. The percentage distribution of nail changes has been presented in table 10.

Table 10: Distribution of cases according to nail changes

Nail changes	N	%
Nail pits	25	100

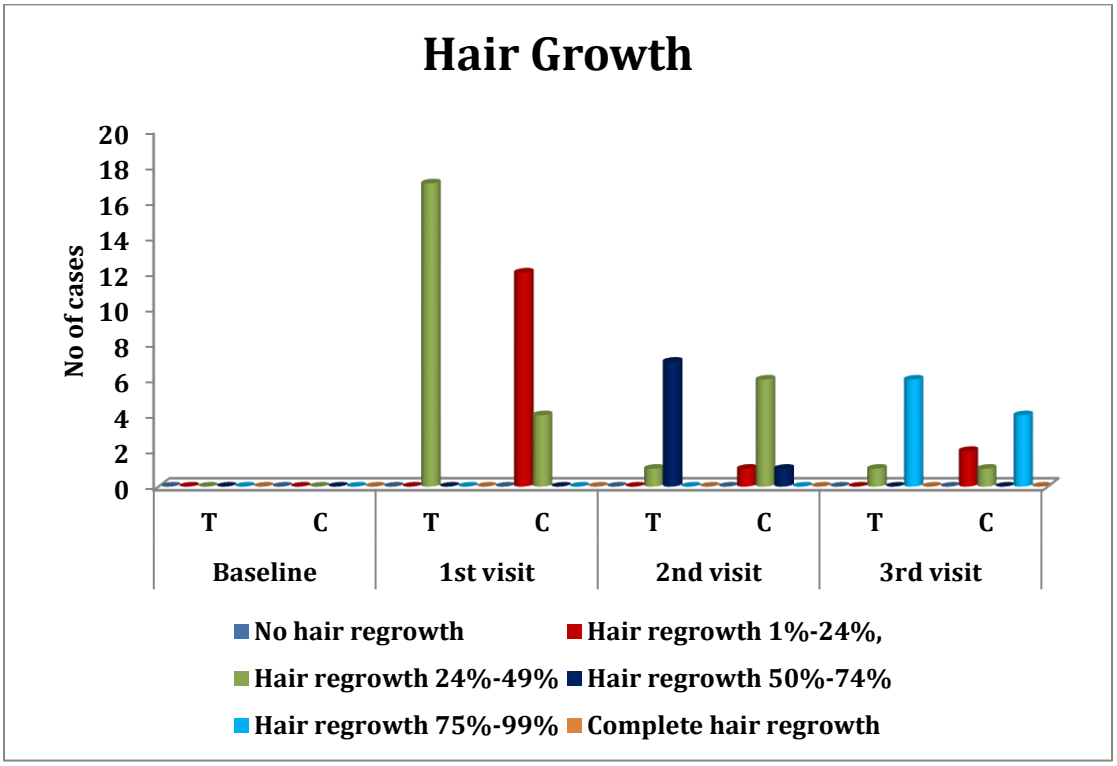
Hair growth:

This study shows that 308-nm excimer lamp induces effective hair regrowth in all patients with alopecia areata partialis. None of these patients lost their hair over a follow-up period of 3 months. Following are the results during follow-up period of 3 months which had 3visits. 1st visit 17 patients had hair regrowth of (24%-49%) at test site and 12 patients had hair regrowth of (1%-24%) at control site. 2nd visit 7 patients had hair regrowth of (50%-74%) at test site and 6 patients had hair regrowth of (24%-49%) at control site. 3rd visit 6 patients at test site and 4 patients at control site had hair regrowth of (75%-99%). The results are summarized in table 11 and figure11.

Table11: Distribution of cases according to hair growth

Growth	Baseline		1st visit		2nd visit		3rd visit	
	T	C	T	C	T	C	T	C
No hair regrowth	0	0	0	0	0	0	0	0
Hair regrowth 1%-24%,	0	0	0	12	0	1	0	2
Hair regrowth 24%-49%	0	0	17	4	1	6	1	1
Hair regrowth 50%-74%	0	0	0	0	7	1	0	0
Hair regrowth 75%-99%	0	0	0	0	0	0	6	4
Complete hair regrowth	0	0	0	0	0	0	0	0

Figure 11: Distribution of cases according to hair growth

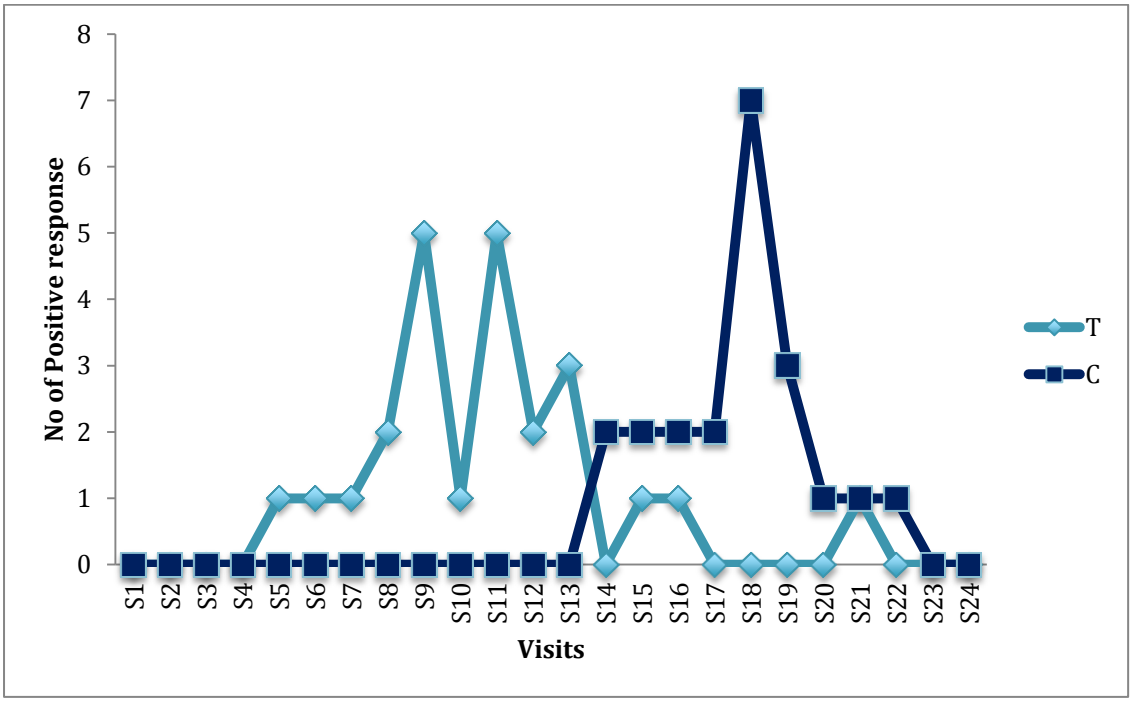


Among 25 patients 6 patient showed complete response to excimer as well as topical fluticasone at the end of 3 month follow-up. But response to excimer lamp therapy was started during 5th session compared to that of topical fluticasone, were hair regrowth was started at 14th session and onwards during a total of 12week treatment period. Table 12 and figure 12 represents the positive response of with with AA to excimer lamp vs topical fluticasone therapy.

Table 12: Distribution of cases according to positive response

Visit	T	C	P value
S1	0	0	-
S2	0	0	-
S3	0	0	-
S4	0	0	-
S5	1	0	<0.001*
S6	1	0	<0.001*
S7	1	0	<0.001*
S8	2	0	<0.001*
S9	5	0	<0.001*
S10	1	0	<0.001*
S11	5	0	<0.001*
S12	2	0	<0.001*
S13	3	0	<0.001*
S14	0	2	<0.001*
S15	1	2	<0.001*
S16	1	2	<0.001*
S17	0	2	<0.001*
S18	0	7	<0.001*
S19	0	3	<0.001*
S20	0	1	<0.001*
S21	1	1	-
S22	0	1	<0.001*
S23	0	0	-
S24	0	0	-

Figure 12: Distribution of cases according to positive response



The clinical and dermoscopic photographs of a patient presented in figure 13a, 13b are baseline images. Figure 13c and 13d are the clinical photographs at the end of 3rd visit (monthy follow-up) after the therapy which shows few vellus hair.

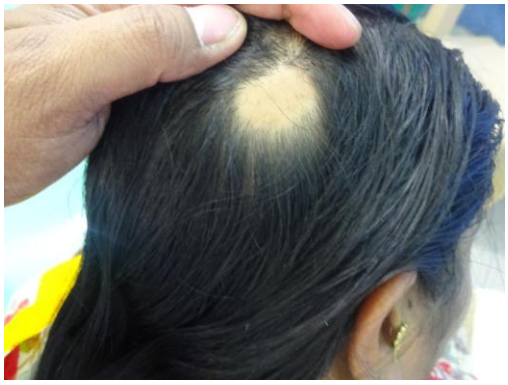


Figure: 13a

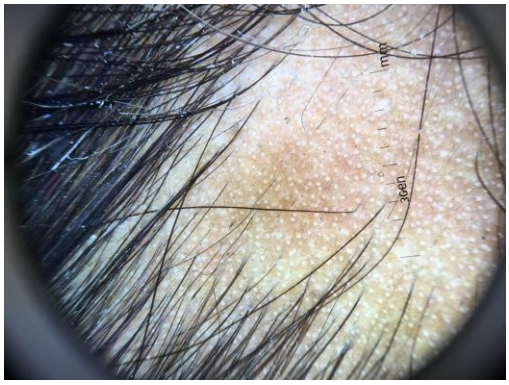


Figure: 13b

Figure: 13c

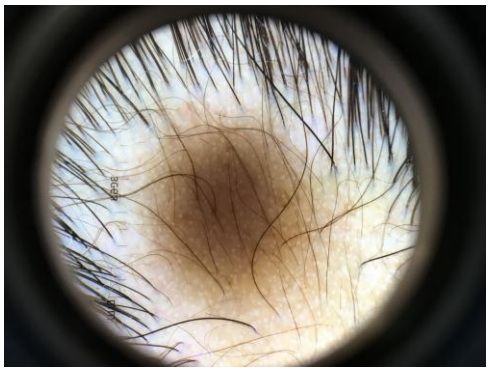


Figure: 13d

The clinical and dermoscopic photographs of a patient presented in figure 14a, 14b, are baseline images of test site and 14e, 14f are baseline images of control site. Figure 14c, 14d and 14g, 14h are the clinical photographs at the end of 3rd visit (monthy follow-up) after the therapy which shows complete regrowth of hair at test site 14c, 14d and hair regrowth score of 3 (50%-74%) at control site.

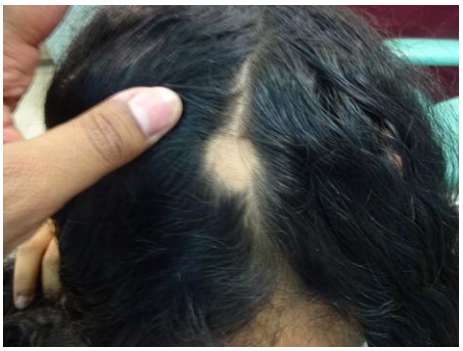


Figure: 14a

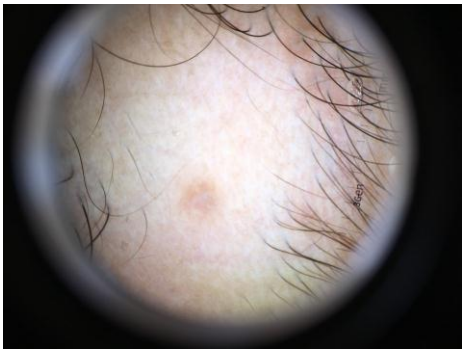


Figure: 14b

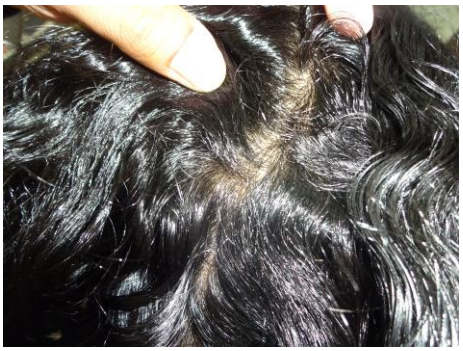


Figure: 14c

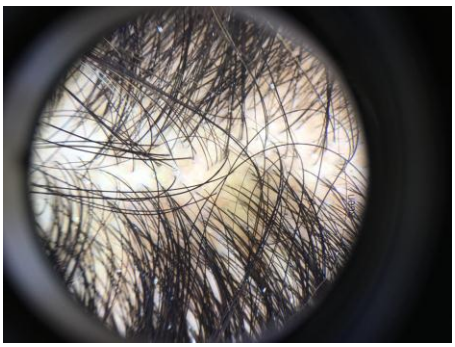


Figure: 14d

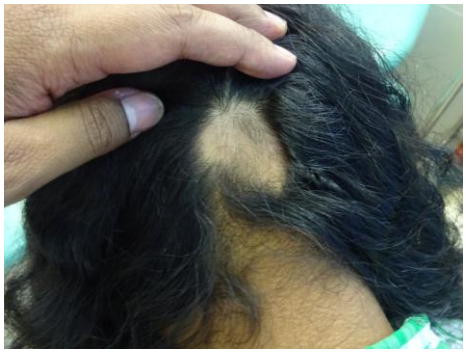


Figure: 14e

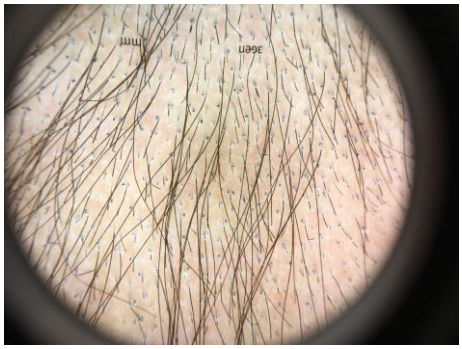


Figure: 14f

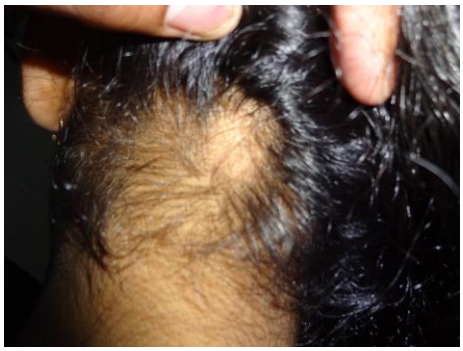


Figure: 14g

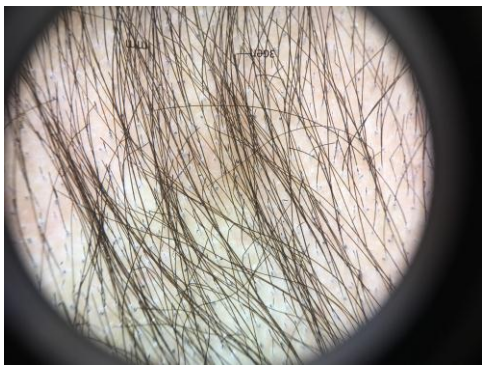


Figure: 14h

The clinical and dermoscopic photographs of a patient presented in figure 15a, 15b, 15c and 15d are baseline images of test and control site. Figure 15e, 15f, 15g and 15h are the clinical photographs at the end of 3rd visit (monthy follow-up) after the therapy which shows complete regrowth of hair at both test and control site.

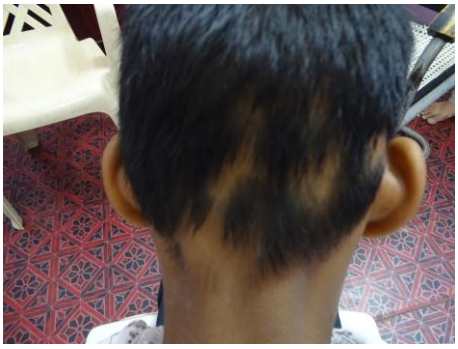


Figure: 15a

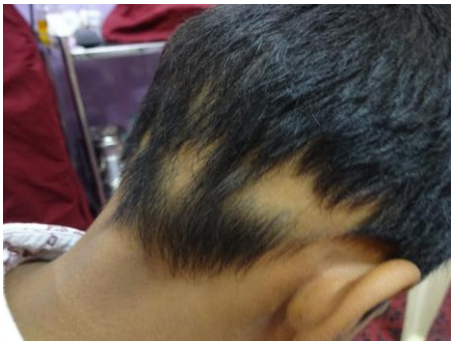


Figure: 15b

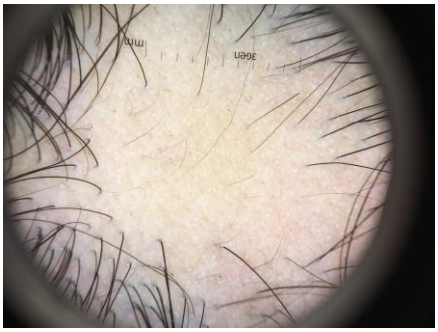


Figure: 15c

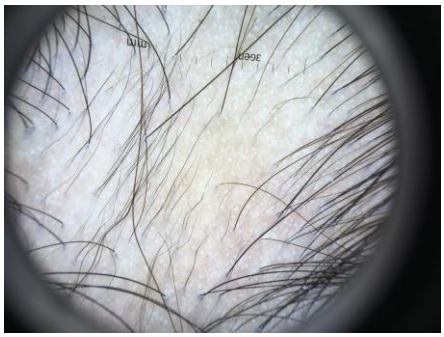


Figure: 15d

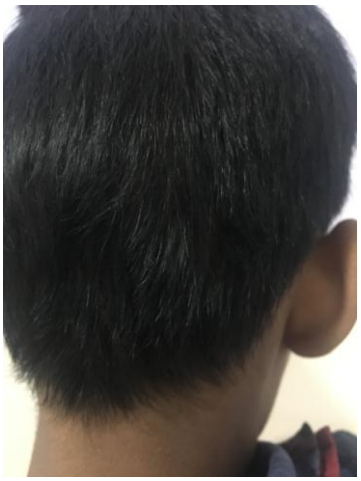


Figure:15e

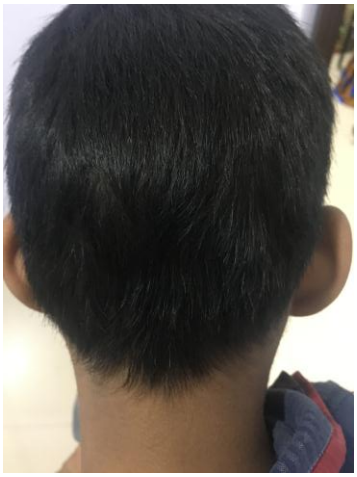


Figure: 15f

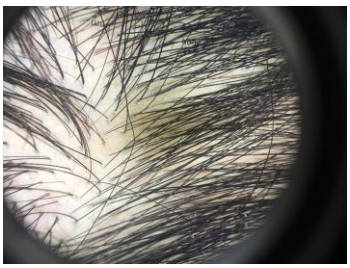


Figure: 15g

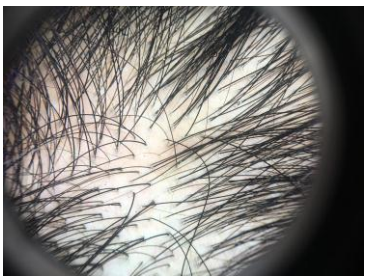


Figure:15h

DISCUSSION

Treatment of AA is a challenge to the dermatologists. As healthy hair is important for the young and attractive appearance of individual in this modern world, the consequences of AA are predominantly psychological. So, the main therapeutic objective is to maintain or induce hair growth activity.

Alopecia areata is thought to be a hair-specific, T-cell-mediated autoimmune disorder, resulting in reversible hair loss.[5] The pathogenesis of alopecia areata is being unravelled with various animal and human studies.[1]

Alopecia areata is often treated with intralesional corticosteroids or contact immunotherapy. However, these treatments have a limited success rate, particularly in cases where there is extensive spread of the lesion. Although systemic corticosteroids are occasionally utilized in the treatment of AA, its usage is limited due to the adverse effects of long-term administration. Localized T-cell-mediated skin disorders are frequently treated by PUVA or narrow-band UV-B (311-nm) phototherapy, which have immunosuppressive effects. Clinical trials of both phototherapy treatments for AA have been conducted with variable success. However, these therapies involve the irradiation of large unaffected areas along with the AA lesions.[3]

On the other hand, the 308-nm excimer lamp radiation allows selective irradiation of the affected area with sparing of the surrounding unaffected skin. Moreover, monochromatic excimer light, which acts specifically on T lymphocytes, keratinocytes and dendritic cells and provokes apoptosis, has the advantage of a lower cost compared with the laser system. Carcinogenicity of phototherapy increases with the cumulative UV dose.[3]

Although the risk assessment concerning the carcinogenicity of narrow-band UV-B is not clearly defined, we presume that the reduced cumulative UV dose needed to treat AA with a 308- nm excimer lamp reduces the risk of carcinogenicity.[3]

In a study by ohtsuki *et al*,[5] that comprised of 3 female patients with single alopecia areata lesions were treated with 308-nm excimer lamp. Their study showed that 308-nm excimer lamp induces effective hair regrowth in patients with a single alopecia areata lesion. None of the patients reported hair loss during the follow up period of 4 weeks. Their therapy seemed to be more effective in treating single alopecia areata lesions compared with conventional narrow-band therapy.

In a study by Ohtsuki *et al*,[20] comprised of 16 patients (4 male and 12 female) with localized or multiple alopecia areata lesions were treated with 308-nm excimer lamp once every two weeks. Hair regrowth was observed in 14 patients. Among them 10 patients showed more than 50% hair regrowth, which suggest that 308-nm excimer lamp is a good therapeutic alternative without serious side effect for treating alopecia areata lesions compared with conventional narrow-band therapy.

Several topical corticosteroids with varying levels of efficacy have been used to treat alopecia areata. They are a good option in children because of their painless application and wide safety margin. Topical corticosteroids are ineffective in alopecia totalis/universalis. Treatment must be continued for a minimum of 3 months before regrowth can be expected and maintenance therapy often is sometimes necessary.[1]

In the present study the male to female ratio was 3:1. There was statistical significance in the gender distribution of AA. The mean (± SD) age of the study population was 22.8 (± 11.8) years.

The location of AA in the present study was on the scalp in 22 (88%) patients, followed by scalp and beard in 3 (12%) patients.

Duration of lesions in the present study was about <1 month in 5 (20%) patients, 1-2 months in 10 (40%) patients, 3-6 months in 4 (16%), >6 months in 6 (24%) patients.

A total of 25 patients were recruited in the present study, 11 of whom completed the treatment duration of 12 weeks, twice weekly of excimer lamp therapy, with total 24 sessions and monthly follow-up of 3 months which included 3 visits each, during which clinical and dermoscopic photographs were taken for hair regrowth assessment. At the control site topical fluticasone cream was applied twice daily for a period of 12 weeks. Of these 11 patients 7 of them had complete regrowth of hair at the test site where as partial hair regrowth at control site compared to the test site, 3 patients dint show any response even at end of the 3 month follow-up at the control site where as partial response was seen at the test site.

The rest 14 patients had irregularly followed up but completed the total 24 sessions of excimer lamp therapy in more than 12 weeks and couldn't make it to the monthly follow-up for the 3months which included 3 visits each. They showed hair regrowth score of 2 (25%-49%), and 3(50%-74%) at the test site where as hair regrowth score of 1 (1%-24%), and 2 (25%-49%) at the control site.

We have also modified our methodology by not taking into consideration the duration of the lesion which should be more than 6 months according to the inclusion criteria, as patients with AA lesions needed to have two or more comparable patchy loss of hair which was difficult in finding the cases for the study.

Hair regrowth was seen in all the patients expect for the 3 patients. Hair regrowth was started at session 5 onwards with excimer lamp and session 14th

onwards with topical fluticasone. Hence, Response with excimer lamp was faster compared to that of topical fluticasone cream.

In our study the excimer lamp therapy was tolerable to all the patients tested. Side-effects observed in different patients were limited to mild erythema, hyperpigmentation and mild itching with both excimer lamp and topical fluticasone cream.

From the above discussion it is evident that excimer therapy is an effective, safe and promising therapeutic modality for the treatment of AA along with topical fluticasone cream. However, the therapeutic response recorded in our study showed difference in group of patients, though statistically superior to response with the excimer lamp compared to that of topical fluticasone cream.

CONCLUSION

Alopecia areata is a frequent disease but with rarer severe forms that provoke important psychosocial consequences to the patients.

It is considered that alopecia areata is an autoimmune disease involving mainly the cellular immunity through the CD8 lymphocytes that act on follicular antigens. Activation of the lymphocytes of the perifollicular infiltrate specific to alopecia areata produces the release of cytokines (IL-1 alpha and beta, TNF) that inhibit the proliferation of cells in the pilar follicle, thereby interrupting the synthesis of hair without destroying the follicle. The process is aggravated by the presence of atopy and probably psychological trauma.

The simple localized forms heal spontaneously or respond to simple treatment, such as corticosteroids either topical or injected locally by infiltration. The severe forms have a reserved prognosis and are difficult to treat, the best results are achieved topical immunotherapy techniques.

Out of 25 patients treated with excimer lamp and topical fluticasone cream, complete response was seen in 11 patients with hair regrowth score of 5 (complete hair regrowth) at test site and score of 3 (50%-74%) and 4 (75%-99%) at control site. 3 patients dint not show any response to the treatment at the control site with score of 0 (no hair regrowth) but partial response with few vellus hair and hair regrowth score of 1 (1%-24%), and 2 (25%-49%) at the test site was observed, partial response was seen in 14 patient with hair regrowth score of 2 (25%-49%), and 3(50%-74%) at the test site where as hair regrowth score of 1 (1%-24%), and 2 (25%-49%) at the control site at the end of 12 weeks.

There was no therapy-related side-effect in any patient. No residual pigmentation or scarring was noted in any patient. No new lesion appeared in any patient during the study period of 12 weeks or during 3 months of follow-up. No recurrence of lesions was seen in any patient while on follow-up for 10 weeks.

The results of this study did not establish "topical fluticasone cream" as a unique therapeutic modality for AA. The results with "excimer therapy" indicated that this therapy induces effective hair regrowth within short duration without any serious side effect for treating AA.

However the study had a small sample size and longer duration of follow-up of the patients. The positive findings were; absence of recurrence of treated AA lesions and no appearance of new lesions at the treated body parts as well as at distant locations. These findings hint towards efficacy of this non-invasive technique in the treatment of AA, especially in children. However, larger, randomized controlled studies are necessary to establish these findings.

LIMITATIONS OF THE STUDY:

Our sample was relatively small and the duration of our study was too long. The study was done within a selected group of sub population and hence may not reflect the actual prevalence in general population.

SUMMARY

A hospital based prospective study to determine the efficacy of 308nm excimer lamp vs topical fluticasone cream in the treatment of alopecia areata was conducted from November 2015 to July 2017. Total 25 patients with alopecia areata were included in the study.

Patients in the 'study' group were offered treatment with excimer lamp twice weekly at test site for 12 weeks and topical fluticasone cream twice daily application over the control site for a period of 12 weeks. Response to treatment in the form of hair regrowth was done by assessment of hair with grading on a 6-point scale at the end of 12 weeks.

Following are the salient observations of the study:

- The mean age (± SD) of the subjects in study group was 22.8 (± 11.8) years.
- The male to female ratio was 3:1.
- Nail changes were noted in all of the patients.
- Family history of AA was present in 16% of the patients
- History of receiving treatment in the past was present in 8 (30.8%) patients and 17 (68%).
- In study group, maximum improvement of hair regrowth with excimer lamp theapy within short duration 5th session onwards was observed compared to topical fluticasone cream where hair regrowth was observed during the 14th session (3rd month) of therapy.
- No therapy-related side-effect was noted in any patient.

- There was no residual pigmentation or scarring.
- No new lesion appeared in any patient during the study period of 12 weeks or during 3 months of follow-up.
- None of the patients showed recurrence while on follow-up for 3 months.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATES

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE

NO/58/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17-11-2015 at 03 pm scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title "A Comparative randomised clinical trail to defer-mine the efficacy of 308 nm excimer lamp Vs topical fluticasone cream in the treatment of alopecia areata"

Name of P.G. Student : Dr Vollala Naresh Kumar.
Dept of Dermatology

Name of Guide/Co-investigator : Dr Arun. C. Inamadar.
Prof & HOD. Dermatology.

DR.TEJASWINI VALLABHA
CHAIRMAN
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization:
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

PROFORMA

SCHEME OF CASE TAKING

B.L.D.E.U's SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, BIJAPUR.

Department of Dermatology, Venereology and Leprosy.

SL NO: Date:

Name:

Age/sex:

Father's/Husband's name: IP NO/ OP NO:

Occupation:

Address: Phone no.

1. Chief complaints:
2. Presenting features:

   Duration of lesion:
3. Any previous treatment received:
4. Past history:

   History of photosensitivity:

   Any associated illness:

   Any treatment history for chronic illness:

   History of Diabetes mellitus:

   Other immunosuppressed states:
5. Family history:

6. General Physical Examination:

Weight:	BP:	Pulse rate:
Pallor:	Cyanosis:	Icterus:
Clubbing:	Lymphadenopathy:	Edema:

7. Cutaneous examination

Site: scalp/ eyebrows / eyelashes / beard/ trunk / arms/ legs / axillae / pubic

Number of scalp lesions: 2-5/ 5-10/ >10

Size:

Type of lesion: patchy alopecia

Nail changes:

8. Systemic Examination

Cardiovascular system :

Respiratory system :

Central nervous system :

Abdominal examination :

9. Diagnosis:

10. Investigations:

Chart 1: Treatment dose and response at test and control sites in each visit.

No of visits	Test site MED mJ/cm^2	Test site response/onset of hair regrowth	Control site response/onset of hair regrowth
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			

Chart 2: Investigator assessment of hair regrowth at test and control sites (at baseline and during three follow up).

	Baseline assessment	1st visit	2nd visit	3rd visit
1.Hair count				
2.Hair density (Wherever necessary)				
3.Hair regrowth Score				

INFORMED WRITTEN CONSENT FORM

B.L.D.E.U's SHRI B M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR-586103

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT : - A COMPARATIVE SELF CONTROLLED CLINICAL TRIAL TO DETERMINE THE EFFICACY OF 308nm EXCIMER LAMP VS TOPICAL FLUTICASONE CREAM IN THE TREATMENT OF ALOPECIA AREATA.

PG GUIDE : - DR ARUN C INAMADAR

PG STUDENT : - DR NARESH KUMAR VOLLALA

PURPOSE OF RESEARCH:-

I have been informed that this project will be studied to measure the psychological impact of vitiligo.

BENEFITS:-

I understand that my participation in this study will help the investigator to study the the efficacy of 308nm excimer lamp vs topical fluticasone cream in the treatment of alopecia areata.

PROCEDURE:-

I understand that relevant history will be taken and I will undergo detailed clinical examination after which necessary investigations will be done whenever required.

CONFIDENTIALITY:-

I understand that medical information produced by this study will become a part of my hospital records and will be subjected to the confidentiality and privacy regulation of the said hospital. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file.

If the data are used for publication in the medical literature or for teaching purposes no names will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand I may see the photographs, videotapes and hear the audiotapes before giving this permission.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:-

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in this study at any time without prejudice. I also understand that Dr Naresh Kumar Vollala may terminate my participation in this study at any time after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician, if this is appropriate.

INJURY STATEMENT:-

I understand that in the unlikely event of injury to me resulting directly from my participation in this study and if such injury were reported promptly, then medical treatment will be available to me, but no further compensation will be provided. I understand that by my agreement for my participation in this study, I am not waiving any of my legal rights.

I have explained to (patient's / relevant guardian's name) the purpose of the research, the procedures required, and the possible risks and benefits to the best of my ability in patient's own language.

I confirm that …….(Name of the PG guide / chief researcher) has explained to me the research, the study procedures that I undergo and the possible risks and discomforts as well as benefits that I may experience. I have read and I understand this consent form. Therefore, I agree to give my consent for my participation as a subject in this research project.

_____	_____
Participant / guardian	Date
_____	_____
Witness to signature	Date

KEY TO MASTER CHART

S. No	-	Serial Number
S1-24	-	Session Number’s
Pa	-	Patchy lesions
NP	-	Nail pits
T	-	Test site
C	-	Control site
+	-	Hair regrowth started during the session
0	-	No hair regrowth
1	-	Hair regrowth (1%-24%)
2	-	Hair regrowth (25%-49%)
3	-	Hair regrowth (50%-74%)
4	-	Hair regrowth (75%-99%)
5	-	Complete hair growth
HC	-	Hair count
HD	-	Hair density
HRS	-	Hair regrowth score