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Review Article

Local Treatments for Alopecia Areata: an Update.

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Abstract:

Alopecia areata (AA) can be defined as a common cause of non-scarring hair loss that may be in the form of different patterns as patchy, confluent or diffuse patterns. AA mostly involves the scalp and also can affect other parts of the skin as beard, mustache or any other hairy areas of the skin. AA is considered a therapeutic challenge and cannot be treated easily due to different reasons as disease prognosis, non-predictable course and variable efficacy of available lines of treatment. AA may have a serious psychological effect on many patients. AA has no direct impact on general health that justifies the use of hazardous treatments particularly of unproven efficacy. Fortunately many patients may experience regrowth of hair spontaneously without use of any treatment. The psychological effects of alopecia that is mainly due to change in body image may have obvious hazardous effects on the patient general health. AA is not easily treated, and unfortunately, no universal totally accepted treatment exists for all cases. As regard a relationship between psychiatric comorbidities, stressful life events, and AA was detected so, adjuvant psychotherapy and support groups should be considered beside the different lines of AA treatment as topical, systemic, intra lesion and phototherapy modalities.

Keywords: Alopecia areata, intralesional pentoxyphyline In AA, Topical immunotherapy in AA.

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Introduction:

Alopecia areata (AA) is classified among the autoimmune diseases as the most common autoimmune disorder. AA is ordered as second cause of hair loss after androgenetic alopecia, that is characterized by hair loss without any scalp scar i.e, healthy scalp. [(1)] As regard prevalence of AA, in general population about 1-2% affected by AA. However, according to a clinical trial studied (100 patients) in Sohag Governorate prevalence of AA represented 26% between all cases of hair loss. [(2)]

In another clinical study conducted in Egypt, the prevalence of AA was 3.1% between new dermatology outpatients. [(3)] As regard relation between AA and sex selection, although some reports suggested a slight increase in females, AA can affect both sexes. [(4)] As regard classification of AA depending on severity and the areas where hair loss is observed, it is classified into three types: AA localisata, total Alopecia and universal Alopecia. [(5)] As regard age most cases of AA reported between 10 and 25 years [about 60%] but also AA appears in children and young adults. [(6)] As regard course of AA wide range of variability is a landmark. The most classic and least resistant form is AA localisata as it spontaneously within 1 year can be resolved, with 40–70% of the patients experiencing spontaneous regrowth without any treatment within a few months. [(7)] Unlike AA localisata, complete

spontaneous hair regrowth with total alopecia or universal alopecia is only 10% or less. [8] The least forms of AA showing improvement include AT, AU, or ophiasis pattern hair loss [poor prognostic factor]. The previous forms of AA are considered as strong predictors of a poor prongosis. [9] Unfortunately treatment of AA is challenging and there is no consensus between authors that there is specific and effective single line of treatment for AA. [10]

Local treatment modalities of AA:

After reviewing literatures as regard different lines of local treatments of AA, we found many lines of treatment with different values of efficacy and safety as we will present in the following paragraphs focusing on the new local lines that reported.

1-Topical corticosteroids:

Topical corticosteroids considered one of the oldest lines of treatment of AA. They are widely used depending on mechanism of actions as their potent anti-inflammatory and immune suppressive effects decreasing damage to hair follicles by aggressive cytotoxic T lymphocytes. In the literatures many conflicting results as efficacy are reported. [11]

Many clinical trials assessed the efficacy and safety of topical steroids in different types, doses and forms showing different results as regard safety and efficacy. [12, 9, 13&14]

2-Topical immunotherapy:

Different guidelines reported that patients with severe resistant AA can be treated with topical immunotherapy. As regard the mechanism of action of topical immunotherapy, although an immunomodulatory effect on per follicular infiltrate plays the key role but is not completely understood. Topical immunotherapy material attract the destructing cytotoxic T lymphocytes away from the affected hair follicles toward the locally applicated immuneotherapy. Weekly application of a strong substance like diphenyl cyclo propenone (DPCP) or squaric acid dibutyl ester (SADBE) on the scalp to produce minute inflamation that finally stimulates hair follicle growth. [15]

Chemically, as regard DPCP formation, bromination of dibenzylketone to form a precursor, (a,a-dibromodibenzylketone). Then the previous precursor is cyclized with a base to form DPCP. Some reports reported about the mutagenicity of that precursor (a,a-Dibromodibenzylketone), so there is a fear of the possibility of its contamination in the DPCP material .[16] Many clinical trials assessed topical immunotherapy as line of treatment. [17]

DPCP is not constant substance and cannot be valid for long time after dissolving and the light destruct DPCP. To avoid degradation of DPCP, the use of dark bottles to protect DPCP from light is recommended. After exposure to ultraviolet radiation (UV) and heat, DPCP is destructed forming diphenylacetylene and carbon monoxide (CO). As its chemical property to absorb light and heat, acetone is considered the standard solvent used to dissolve DPCP powder protecting the DPCP fromdegradation.[18]

In 1983, Happle reported about the method by which we can use DPCP. After dissolution of DPCP powder, Happle recommend to applicate DPCP solution in a concentration 2% to a small area of the skin mostly scalp with a size of application not more than 4x4 cm on the scalp. The substance washed out after 48 hours to induce sensitization**.** Two weeks later, treatment can be started with administration of DPCP to the affected areas. It is recommended to start with a concentration that induces a mild inflammation of the scalp. After 24 hours, washing out of the scalp is recommended. Sun exposure is better to be avoided during the presence of the topical immunotherapy substance over the skin. [19]

If there was no response (hair regrowth) after six months, the patient is considered as non-responder to DPCP and the therapy must be discontinued. Long time is required as 12-18 months of therapy length before confirming the result of DPCP as good response may occur very late after years. Extension of treatment is useful as reported in the literatures, about one third of patients show good response after 6 months of treatment and can reach about two thirds of patients after 32 months of treatment. [20]

As regard safety of topical immunotherapy generally and DPCP specifically, induction of a marked inflammation characterized by vesicular lesions is

the main adverse effect of this treatment and sometimes large bullae may develop. If that adverse effect occurred, the topical immunotherapy substance should be removed from the skin by washing and treatment with a topical corticosteroid should be started. Also, occipital and or cervical lymphadenopathy is considered a common adverse effect of topical immunotherapy. Some authors reported that vitiligo, urticarial & dyschromia are possible side effects. Although there is no solid data about use of DPCP during pregnancy and lactation, it is better to avoid treatment with pregnancy and lactation. [21]

3-Topical minoxidil:

Minoxidil is usually used as adjuvant and not alone as a line of treatment for AA. Minoxidil is considered as a vasodilator drug. It is used in the form of oral tablet in treatment of hypertension. For its use in treatment of hair loss, different forms of topical minoxidil as solution, gel and foam are used to help hair growth. As regard the mechanism of action of minoxidil in hair regrowth, it stimulates hair regrowth throw many different routes without affection of hair cycle. [22]

Minoxidil increases blood supply surrounding the hair follicles improving the nutritional environment around them. Interactions between the bulb of the hair follicle and the vascular bed below are responsible for conversion of hair follicles from an inactive telogen stage to a growing anagen stage. [22]

Many clinical trials assessed the efficacy and safety of topical minoxidil in different doses and forms in treatment of AA. [21&22]

4-Anthraline:

Anthraline is considered as a method for topical immunotherapy. Anthraline induces irritant local dermatitis. Modulation of the expression of cytokines represents the mechanism of action of anthralin. The efficacy of topical anthralin in the treatment of AA either alone or in combination was found in a few controlled trials. Erythema, oedema and pain are common side effects of anthralin especially in face or when exposed to the sun. [23]

5- Tacrolimus:

As regard mechanism of action tacrolimus is considered as calcineurin inhibitor that acts locally in the skin throw inhibition of T-cell activation preventing production of several cytokines as IL-2, IFN-gamma and TNF-α. In animal studies tacrolimus treated alopecia in mice. Although in patients with severe cases of AA, conflicting results with topical tacrolimus was reported. [24]

6- **Topical retinoid**:

Topical retinoids are not used alone but in combination with other lines of treatment to treat AA. The exact mechanism by which topical retinoid improve AA is not well known. Many theories state that inflammation produced by topical retinoid that might increase the hair growth in AA. Also, another theory that tretinoin may promote vascular proliferation. Topical retinoid also may promote and regulate cell proliferation and differentiation in the epithelium. [25]

All these mechanisms are important theories for AA treatment but the exact mechanism by which topical retinoid improve AA and induce hair regrowth is not completely understood. As regard efficacy and safety of topical tretinoin, they were assessed by many investigators either alone or in comparative manner with other lines of treatment showing different responses with different types of AA with minimal side effects. [25]

7-Topical prostaglandin analogue:

The ophthalmologists noticed that the use of anti-glaucoma eye drops containing prostaglandins was followed by increase in growth of eyelashes as a usual side effect. [26]

FDA approved administration of prostaglandins topically in treatment of AA mainly bimatoprost. Bimatoprost is a prostaglandin similar that caused increase in growth of eyelashes when used by ophthalmologists in treatment of glaucoma. It acts throw the activation of the anagen (growing) stage of hair follicles. [27] Many trials assessed the efficacy of prostaglandin analogues in treatment of AA. [28&29]

8- Topical vitamin D analog:

The exact underlying mechanism of topical vit. D analogues to treat AA is not well known. Many author suppose vitamin D acts as supporting to the HF by preventing the secretion of IFN-γ;, atten-

uation or prevention of the autoimmune effects that cause AA. This occurs through regulation of many cells as the auto reactive effector T cells and mast cells preventing cytotoxic T lymphocytes from damaging effects. [30]

Also inhibition to JAK/STAT pathway is reported as another theory for the mechanism of action. This occurs through prevention of production of damaging cytokines related to AA. As regard efficacy and safety, many authors preferred use of topical vit. D analogues in treatment of mild cases of AA especially due to minimal side effects even though fair response in hair regrowth. [30]

9-Intralesionalcorticosteroids:

Glucocorticoids are characterized by their immune-suppressive effects. They are used in treatment of many immunological disorders especially AA. Topical administration of glucocorticoids is preferred than systemic administration due to side effects especially when used in high doses for long duration. So, intra lesion corticosteroid injection is a treatment of choice for all types of AA especially AA localisata. [31]

Many types of glucocorticoids present in market, the most suitable for intra lesion injection is triamcinolone acetenoide. Triamcinolone acetonide is recommended to be injected in diluted concentrations 1/8 – 1/4. These diluted concentration equal to about 5-10 mg/ml. It is recommended to be injected 0.1 mL of solution into multiple sites 0.5 – 1 cm apart into the deep dermis using a 30 gauge needle. [31]

As regard efficacy of intra lesion injections of steroids in AA, excellent response of hair growth in AA was reported. As regard side effects, minimal side effects in comparison to systemic administration. But also no one can deny that multiple injections in the skin in that manner that may reach 100 injections in extensive cases are so painful making some patients refuse that method of treatment. [32]

As regard its action, it is a strong inhibitor to inflammation and immune suppressive drug. It is considered a corner stone in treatment of AA. [32]

10-Intralesional methotrexate:

That immune suppressive and anti-proliferative drug used systemically either injections or by oral route in treatment of many immune disorders and tumors. Recently it was used by intra lesion injection method for treatment of AA. As regards efficacy intra lesion injection of methotrexate is considered good treatment line. [33]

As regard safety in comparison with systemic MTX where hematologic and hepatic adverse events may occur, they are less with intra lesion injection. Moreover, there was no atrophy that may occur with intra lesion corticosteroid. There are only local adverse effects such as hyperpigmentation, erosions and erythema **.**[33]

11-Intralesional pentoxyphilin:

Pentoxiphylline is considered as phosphodiesterase inhibitor that acts without selection. As regard its mechanism of action pentoxifylline affects cyclic ad enosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) causing large change in the inflammatory process. With more details as regard the modulation of inflammation, Pentoxifylline acts through inhibition of release of many inflammatory cytokines (e.g., IL-1, IL-6, and IL-8)**.** [34]

It acts through inhibition of T lymphocytes activation and adhesion of T lymphocytes throw decrease in ICAM-1 on cell surfaces. That then prevents toxicity to cells that occurred through NK cells. It has been reported to be effective in localized AA. More trials are needed either alone or in combination with other lines of treatment of AA. [34]

12- Platelet-rich plasma (PRP):

Platelets with high concentrations from certain individual plasma are defined as Platelet-rich plasma (PRP). PRP promotes the growth of tissues and HFs as it is rich source for many growth factors and cytokines. As regard mechanism of action, there is no definite mechanism of action, but many theories are supposed. [35]

PRP can activate extracellular signal–regulated kinase (ERK) and Akt signaling pathways increasing the growth of HF cells (DPCs). Also, it interferes with apoptosis. Also increasing the expre-

ssion levels of β-catenin and FGF-7 has a role. Also, PRP contribute to effectiveness for AA through inhibition of inflammation by decreasing MCP-1 expression and increasing TGF-β expression. [35] Many clinical trials assessed the use of PRP as a line of treatment for AA. [36-38]

13- Stem cells:

Recently many authors talk about use of stem cells in treatment of AA. Stem cells are considered a part of regenerative medicine that is a recent with good results in treating many diseases as AA. As positive outcomes, it is recommended to be used instead of usual therapies. As its safety, stem cells considered as promising line to treat AA needing further clinical trials in the future. [39]

As regard mechanism of action, they act throw paracrine and trophic effects as their secretions especially growth factors as VEGF, insulin-like growth factor (IGF), interleukin-6 (IL-6) and other cytokines. That act through Want signaling pathway induction throws different proteins secreted by dermal papilla cells (DPCs) as their nourishment by GFs. [39]

14- Photo chemotherapy:

Photo chemotherapy includes many different modalities as PUVA (psoralen and UVA) that include topical PUVA and oral PUVA, photodynamic therapy and extracorporeal phototherapy. Topical PUVA is one of lines of treatment used to treat many dermatological diseases with immunological background as AA. As regard the mechanism of action, many authors reported that both anti proliferative and immunomodulatory effects are involved in treatment of AA and other autoimmune diseases but the exact completely understood mechanism is not proved. [40]

As regard efficacy, the success rate for topical (PUVA) between 15% to more than 70% in many clinical trials [40] There are many routes of administration of topical PUVA for AA as PUVA turban. PUVA turban is a route to introduce psoralen in a diluted nature i.e, solution (8-methoxypsoralen 0.0001%) selectively to the scalp for certain time not exceeds 20 minutes. Then exposure of ultraviolet A radiation to the patient's scalp. [41]

Two or three administrations of topical PUVA every week is recommended by authors. Efficacy of that PUVA is high reaching 70 %. [42] As regard recurrence after improvement only 26% developed relapse. As regard side effects, there are no systemic side effects in comparison to oral PUVA and recommended being used instead systemic route. [40]

15- Excimer laser:

308 nm wave length UVB (excimer laser) is approved to be used in many dermatological diseases as psoriasis, vitiligo and AA. As regard method of action it is not exactly known ,but authors suppose that 308 wave length laser is immune modulator in the affected areas of AA similar to corticosteroids. Also, excimer laser induces T cell apoptosis destructing damaging cytotoxic CD8 T lymphocytes protecting hair follicles from damage. [43]

308 nm wave length is the light emitted by excimer laser. The results of the excimer laser's light on the treated skin induce erythema. [43] As regard efficacy in a clinical trial that included treatment of 42 AA patches with excimer laser, response was observed in 41.5% of patches. During the second month of therapy response starts to appear. Control patches show no response. [44]

Many authors recommend administration of laser therapy sessions twice every week. As regard side effects, excimer laser is well tolerated except erythema at the treated sites. [44]

Paradoxical hypertrichosis is an adverse effect after use of laser hair reduction so, the use of fractional photothermolysis laser phototherapy for the treatment of AA was supposed. Although the route by which laser phototherapy work is not clear, photobiostimulation is supposed theory. The therapeutic effects of these different lasers have been studied in many clinical trials with evidence of good response. [45] Also wounds induced by laser and wound healing may be associated with follicular neogenesis and so hair growth. This is considered as novel theory for mechanism of action that needs further clinical trials. [46]

An embryonic hair phenotype response was observed followed by hair follicles developing**.** In a single case report, good response was observed with fractional laser. It is recommended to encourage

randomized controlled trials with large sample size. [47]

17- Superficial cryotherapy:

Unlike the usual process of cryotherapy with using of liquid nitrogen, superficial cryotherapy is different. It can be defined as exposure of tissue to hypothermic substance (cryogen) for a short time 3-9 seconds. Unlike usual cryotherapy, no crystal formation or blood flow occlusion occurs as the limited exposure to the cryogen in superficial cryotherapy. [48]

In the literatures, liquid nitrogen as a substance for cryotherapy was used in treatment of different types of AA. As regard of efficacy, variable rates of good response were reported. [49]

Recently in 2021, Aboeldahab et al made a clinical study about the therapeutic efficacy and safety of superficial cryotherapy using dimethyl ether and propane (DMEP) mixture with micro needling for mild alopecia areata (AA) in a comparative manner. SALT score was used as a method of assessment showing an excellent response in 15 (37.5%) patients. A good response was reported in 23 (57.5%) patients. [49]

As regard mechanism of action, superficial cryotherapy increases the growth of hair in the AA by different mechanisms. Significant local vasodilatation occurs, leading to increase in blood supply to the affected areas. Then reactive vasodilatation occurs making the blood supply better. Destruction of the keratinocytes, mainly the antigenic components of the HF keratin 16 and trichohyalin that are targeted by antibodies decreasing the infiltrates around HF. Also alteration in immune-logic processes by decreasing the function of Langerhans cells that is present in large numbers in active AA. [1]

As regard side effects, no serious adverse effects were reported. Superficial cryotherapy is considered a well-tolerated, convenient and simple maneuver. Some side effects were reported with the use of superficial cryotherapy as development of vesicles. Sometimes erosion & crust formation may develop. Change in pigmentation may occur rarely. Fortunately these side effects were transient and reversible. Intolerance to cold was reported to be a contraindication to superficial cryotherapy. [1]

18- Micro needling:

Recent emerged procedure is micro needling that is defined as, rolling with miniature fine needles through superficial and controlled puncturing of the skin that is considered a minimally invasive maneuver. As regard mechanism of action, micro needling changes the local immune cells throw induction of hair regrowth by activation of stem cells in the hair bulge of hair follicles and release of different growth factors, enhancing the blood flow to the hair follicles. [49]

Also in 2021, Aboeldahab et al reported by using SALT score in a clinical trial an excellent response in 14 (35%) participants, while a good response was reported in 21 (52.5%) patients in the abovementioned clinical trial. As regard adverse effects, micro needling is relatively safe and well tolerated method of treatment of AA apart from pain during the process of puncturing of the skin. [49]

References:

1-Nada EA, Assaf HA, Aboeldahab SH, Gouda ZA. Superficial cryotherapy, does it work in alopecia areata? SOHAG MEDICAL JOURNAL. 2021 : 25 : 42 - 46.

2-Abd El Meged MM. Patterns of hair loss at SohagUniversity Hospital hair clinic. Sohag Medical Journal. 2019 : 23. 43 - 46.

3-Elshahat Farag Ahmed, Mamdouh Morsy Abdelgawad, Hanan Fathi and Yousef Elbayoumi. Alopecia areata in Egypt : Clinical features and associations. The Gulf Journal of Dermatology and Venereology. 2012: 19 : 1. 9.

4-Qi J. and Garza LA. "An overview of alopecias". Cold Spring Harb Perspect Med.2014: 4 : 371 – 380.

5- Haida Y, Ikeda S, Takagi A. Association analysis of the HLA-C gene in Japanese alopecia areata. Immunogenetics. 2013; 65 : 553-7.

6- Alves R and Grimalt R. Hair loss in children.Curr Probl Dermatol. 2015; 47:55-66.

7- Spano F and Donovan JC. Alopecia areata: Part1: pathogenesis, diagnosis, and prognosis. Can Fam Physician. 2015; 61:751-5.

8- Alkhalifah A, Alsantali A, Wang E, McElwee KJ and Shapiro J. Alopecia areata update: part I and II. Clinical picture, histopathology,pathogenesis and treatment. J Am Acad Dermatol. 2010; 62:177–188.

9- Tosti A, Iorizzo M, Botta GL. and Milani M. Efficacy and safety of a new clobetasol propionate 0.05% foam in alopecia areata: a randomized, double-blind placebo-controlled trial. J Eur Acad Dermatol Venereol. 2006 ; 20 :1243-7.

10- Wolff H, Fischer TW. And Blume-Peytavi U. The Diagnosis and Treatment of Hair and Scalp Diseases. Dtsch Arztebl Int. 2016 ; 113 : 377-86.

11- Delamere FM, Sladden MM, Dobbins HM. and Leonardi-Bee J. Interventions for alopecia areata. Cochrane Database Syst Rev. 2008; 2 : 441-3.

12- Charuwichitratana S, Wattanakrai P. and Tanrattanakorn S. Randomized double-blind placebo-controlled trial in the treatment of alopecia areata with 0.25% desoximetasone cream. Arch Dermatol. 2000 ; 136 :1276-7.

13- Mancuso G, Balducci A, Casadio C, Farina P, Staffa M, Valenti L. and Milani M. Efficacy of betamethasone valerate foam formulation in comparison with betamethasone dipropionate lotion in the treatment of mild-to-moderate alopecia areata: a multicenter, prospective, randomized, controlled, investigator-blinded trial. Int J Dermatol. 2003 ; 42 :572-5.

14- Tosti A, Piraccini BM, Pazzaglia M. and Vincenzi C. Clobetasol propionate 0.05% under occlusion in the treatment of alopecia totalis/universalis. J Am Acad Dermatol. 2003 ; 49 :96-8.

15- Rokhsar CK, Shupack JL, Vafai JJ. and Washenik K. Efficacy of topical sensitizers in the treatment of alopecia areata. J Am Acad Dermatol. 1998; 39:751–61.

16- Wilkerson MG, Henkin J, Wilkin JK. and Smith RG. Squaric acid and esters: analysis for contaminants and stability in solvents. J Am Acad Dermatol. 1985 ; 13: 229– 234.

17- Lee S, Kim BJ, Lee YB. and Lee WS. Hair Regrowth Outcomes of Contact immunotherapy for Patients With alopecia areata: a Systematic review and Meta-analysis. JAMA Dermatol. 2018;154 :1145–51.

18- Buckley DA. and Du Vivier AW. The therapeutic use of topical contact sensitizers in benign dermatoses. Br J Dermatol. 2001;145:385– 405.

19- Happle r, Hausen Bm. and Wiesner-menzel l. diphencyprone in the treatment of alopecia areata. acta derm Venereol. 1983; 63: 49 – 52.Hordinsky M, Ericson M. Autoimmunity: alopecia areata. J Investig Dermatol Symp Proc. 2004 ; 9 :73–8.

20- Wiseman MC, Shapiro J, MacDonald N. and Lui H. Predictive model for immunotherapy of alopecia areata with diphencyprone. Arch Dermatol. 2001;137:1063–8.

21- Messenger A.G., McKillop J., Farrant P., McDonagh A.J. and Sladden M. British Association of Dermatologists' guidelines for the management of alopecia areata. BJD May 2012: 166: 916-926.

22- A.G. Messenger, J. McKillop, P. Farrant, A.J. McDonagh and M. Sladden. Guidelines for the management of alopecia areata. British Journal of Dermatology 2003; 149: 692–699.

23- Adel Alsantali. Alopecia areata: a new treatment plan. Clin Cosmet Investig Dermatol. 2011; 4: 107–115.

24- Gilhar A, Kalish R. Alopecia areata: a tissue-specific autoimmune disease of the hair follicle. Autoimmunity Rev. 2006; 5: 64–69.

25- Das S, Ghorami RC, Chatterjee T. and Banerjee G. Comparative assessment of topical steroids, topical tretenoin (0.05%) and dithranol paste in alopecia areata. Indian J Dermatol. 2010;55:148–149.

26- Bearden W. and Anderson R. Trichiasis associated with prostaglandin analog use. Ophthal Plast Reconstr Surg. 2004;20:320–322.

27- Chanasumon N, Sriphojanart T. and Suchonwanit P. Therapeutic potential of bimatoprost for the treatment of eyebrow hypotrichosis. Drug Design, Development and Therapy. 2018; 12:365-372.

28- Ross EK, Bolduc C, Lui H. and Shapiro J. Lack of efficacy of topical latanoprost in the treatment of eyebrow alopecia areata. J Am Acad Dermatol. 2005;53:1095–1096.

29- Coronel-Perez IM, Rodriguez-Rey EM. and Camacho-Martinez FM. Latanoprost in the treatment of eyelash alopecia in alopecia areata universalis. J Eur Acad Dermatol Venereol. 2010 ; 24 : 481 – 485.

30- Lin X, Meng X and Song Z. Vitamin D and alopecia areata: possible roles in pathogenesis and potential implications for therapy. Am J Transl Res. 2019; 11: 5285–5300.

31- Ferrando J and Moreno-Arias GA. Multi-injection plate for intralesional corticosteroid treatment of patchy alopecia areata. Dermatol Surg. 2000; 26 :690–691.

32- Devi M, Rashid A. and Ghafoor R. Intralesional triamcinolone acetonide versus topical betamethasone valearate in the management of localized alopecia areata. Journal of the College of Physicians and Surgeons–Pakistan. 2015 ; 25 :860-862.

33- Abdelsalam SS, Hamdino M and Darwish HM. Efficacy of intralesional methotrexate in the treatment of alopecia areata. Sci J AlAzhar Med Fac Girls. 2021;5 : 549 – 54.

34- El-Taweel AI and Akl EM. Intralesional pentoxifylline injection in localized alopecia areata. J Cosmet Dermatol. 2019; 18: 602– 607.

35- Almohanna HM, Ahmed AA, Griggs JW, Tosti A. Platelet-rich plasma in the treatment of alopecia areata: a review. J Investig Dermatol Symp Proc.2020. 20: S45–S49.

36- Trink A, Sorbellini E, Bezzola P, Rodella L, Rezzani R, Ramot Y, Rinaldi F. A randomized, double-blind, placebo- and active-controlled, half-head study to evaluate the efects of platelet-rich plasma on alopecia areata. Br J Dermatol. 2013. 169 : 690– 694.

37- El Taieb MA, Ibrahim H, Nada EA, Seif Al-Din M. Platelets rich plasma versus minoxidil 5% in treatment of alopecia areata: a trichoscopic evaluation. Dermatol Ther. 2017. 30. 38.

38- Khademi F, Tehranchinia Z, Abdollahimajd F, Younespour S, Kazemi-Bajestani SMR, Taheri K. The efect of platelet rich plasma on hair regrowth in patients with alopecia areata totalis: A clinical pilot study. Dermatol Ther. 2019. 32. 4 – 12.

39- Salhab O, Khayat L & Alaaeddine N. Stem cell secretome as a mechanism for restoring hair loss due to stress, particularly alopecia areata: narrative review**.** Journal of Biomedical Science . 2022 . 29 : 77 3415 – 3443.

40- Mohamed Z, Bhouri A, Jallouli A, Fazaa B, Kamoun MR. and Mokhtar I. Alopecia areata treatment with a phototoxic dose of UVA and topical 8-methoxypsoralen. J Eur Acad Dermatol Venereol. 2005;19(5):552–555.

41- Broniarczyk-Dyla G, Wawrzycka-Kaflik A, Dubla-Berner M. and Prusinska- Bratos M. Effects of psoralen-UV-A-Turban in alopecia areata. Skinmed. 2006;5(2):64–68.

42- Behrens-Williams SC, Leiter U, Schiener R, Weidmann M, Peter RU. and Kerscher M. The PUVA-turban as a new option of applying a dilute psoralen solution selectively to the scalp of patients with alopecia areata. J Am Acad Dermatol. 2001 ; 44 (2):248–252.

43- Cuneyt Gundogan, Ba¨rbel Greve and Christian Raulin. Treatment of Alopecia Areata With the 308-nm XenonChloride Excimer Laser: Case Report of TwoSuccessful Treatments With the Excimer Laser. Lasers in Surgery and Medicine.2004: 34:86–90.

44- Al-Mutairi N. 308-nm excimer laser for the treatment of alopecia areata. Dermatol Surg. 2007;33(12):1483–1487.

45- Leavitt M, Charles G, Heyman E, Michaels D. HairMax LaserComb laser phototherapy device in the treatment of male androgenetic alopecia: a randomized, double-blind, sham device-controlled, multicentre trial. Clin Drug Investig. 2009: 29(5):283–292

46- Levy V, Lindon C, Zheng Y, Harfe BD, Morgan BA. Epidermal stem cells arise from the hair follicle after wounding. FASEB J. 2007: 21(7):1358–1366.

47- Yoo KH, Kim MN, Kim BJ. and Kim CW. Treatment of alopecia areata with fractional

photothermolysis laser. Int J Dermatol. 2010;49(7):845–847.

48- **Pimentel C, Moraes A, and Cintra M**: Angiogenic effects of cryosurgery with liquid nitrogen on the normal skin of rats, through morphometric study. A Bras Dermatol. 2014;89(3):410-413.

49- **Aboeldahab S, Nada EA, Assaf HA, Gouda ZA, Abu El-Hamd M.** Superficial cryotherapy using dimethyl ether and propane mixture versus micro needling in the treatment of alopecia areata: A prospective single-blinded randomized clinical trial. Dermatologic Therapy. 2021;34:e15044