Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol.(8) Issue(10) (2023), (93-97) **online : ISSN 2356–976x**
http://bjas.bu.edu.eg

Intralesional Injection of Triamcinolone Acetonide, Methotrexate and Vitamin D in Treatment of Alopecia Areata: A Narrative Review

Yossra.M.Mostafa, Asmaa.M.Al Refaei and Karem.T.khalil
Dermatology, Venereology and Andrology Dept., Faculty of Medicine, Benha University
E-mail: yossram686@gmail.com

Abstract
Background: Alopecia Alopecia areata (AA) is a non-scarring autoimmune condition that affects a large percentage of women. The most effective therapy is the intralesional administration of corticosteroids. The immunosuppressive action of the folic acid antagonist methotrexate is quite effective in individuals with severe AA. Hair follicles have high levels of vitamin D receptors, and keratinocytes must express these receptors to keep the hair growth cycle regular. Our goal is to learn more about the potential benefits of injecting Triamcinolone Acetonide (TrA), Methotrexate (MTX), and vitamin D3 directly into AA lesions. Intralesional injections of TrA, MTX, and vitamin D for the treatment of AA up to 2022 were studied by searching and analysing Medline databases (Pub Med and Medscape). The papers that were included in the meta-analysis were chosen based on a strict set of criteria. If they met any of the following criteria, we considered them for inclusion: First, it must be written in English. 2. Appear in journals with a strict peer review process. Third, analyse the benefits of injecting TrA, MTX, and vitamin D into the affected joint to treat AA. Extraction of Data: Research Studies were not included if they did not meet the inclusion criteria. The quality of a study may be determined by checking its ethical approval, eligibility criteria, controls, information, and evaluation methods. Our concerned research results were captured by independently abstracting data utilising a data collecting form from each qualifying study. We conclude that intralesional MTX and vitamin D3 may be safe and effective therapeutic alternatives to intralesional TrA for the treatment of localised AA in adult patients. Hair regrowth and the loss of AA-specific trichoscopic characteristics might both be detected at earlier stages thanks to trichoscopy's usefulness.

Keywords: triamcinolone acetonide, methotrexate, vitamin d, and alopecia areata.

Introduction:

Alopecia Areata (AA) is an autoimmune condition that causes hair loss by primarily damaging hair follicles (HF) during the anagen phase of the hair cycle, although it does not leave scars. Two percent of the world's population has AA. The incidence of AA is higher in children than in adults, is on the rise, and varies greatly among regions (1).

AA manifests itself most often as discrete spots of hair loss on the scalp and elsewhere. Although AA may heal on its own, it is still considered to be a medical emergency in most cases (2).

Immune-suppressing medications like corticosteroids (topical, intralesional, systemic), immunomodulatory treatments like siphenylcyclopropenone, and other choices like Anthralin or Minoxidil have all been described as therapeutic methods for AA. Fewer than 20% of patients achieve full and long-lasting hair regrowth, however, making AA a challenging illness to treat (3).

The immunosuppressive action of the folic acid antagonist methotrexate is quite effective in individuals with severe AA. Side effects and the necessity for monthly monitoring are associated with systemic methotrexate. A safer alternative is intralesional injection or topical treatment (4).

Multiple autoimmune illnesses, including AA, have been linked to vitamin D deficiency. Hair follicles have high levels of vitamin D receptors, and keratinocytes must express these receptors to keep the hair growth cycle regular. It plays a part in the management and regulation of the immune system (5).

The Components and Techniques:

The literature on the effectiveness of intralesional injections of triamcinolone acetonide, methotrexate, and vitamin D for the treatment of AA up to 2022 was gathered by a systematic search of the Medline databases (Pub Med and Medscape).

The papers that were included in the meta-analysis were chosen based on a strict set of criteria. If they met any of the following criteria, we considered them for inclusion: 1) It is written and published in English. 2) Featured in reputable, academic publications. Thirdly, go through the use of Triamcinolone Acetonide, Methotrexate, and Vitamin D as intralesional injections for the treatment of AA.

Extraction of Data: Research Studies were not included if they did not meet the inclusion criteria. The quality of a study may be determined by checking its ethical approval, eligibility criteria, controls, information, and evaluation methods. Our concerned research

results were captured by independently abstracting data utilising a data collecting form from each qualifying study.

A Look Back at the Research:

Patchy Hair Loss

Alopecia areata is a non-scarring kind of hair loss caused by an autoimmune disorder that is mediated by T cells. In spite of the fact that the pathophysiology of AA has been hypothesised to include a complex interaction between loss of immune privilege in the hair follicle, autoimmune-mediated hair follicle destruction, and activation of inflammatory pathways, the exact cause of this condition is still unclear (6).

Several treatment options for AA have been documented. Intralesional corticosteroids are recommended for people whose atopic eczema (AA) affects less than half of their scalp. After that, treatments like minoxidil and anthralin are applied to the scalp (7).

When comparing the SALT scores of patients before treatment, after 12 weeks of therapy, and at the 3-month follow-up, Hamdino et al. (2022)8 found no statistically significant difference between the intralesional MTX and TrA groups. When comparing the SALT score before treatment to the SALT score after the 3-month follow-up, however, there were statistically significant differences between the MTX group and the TrA group. At the conclusion of the 12-week treatment period, the TrA group also had a higher regrowth score than the MTX group had.

Intralesional TrA works primarily by inhibiting the immune system, namely the T-cell-mediated immune response that attacks hair follicles. Because of its reduced potential to cause tissue atrophy, TrA is the corticosteroid preparation of choice. Patchy, localised AA is best treated with intralesional TrA. The intralesional approach circumvents the skin's natural defences, carries the medication straight to the affected location, and reduces the risk of systemic adverse effects. When contrast to the topical approach, medication penetration is more demonstrative (9).

Abdelsalam et al. (2021)10 evaluated the efficacy of intralesional MTX in treating localised AA and found a response rate of around 93.3%. In addition, 15 patients (50.0%) had regrowth of 75% or more. The regrowth scale at the conclusion of the sessions was significantly different from the regrowth scale after 4, 8, and 12 weeks of follow-up.

Despite the long history of intralesional Methotrexate (MTX) usage in dermatology, its potential may not yet be completely recognised or used. It has been shown to be beneficial for a variety of skin disorders. Keratoacanthomas, squamous cell carcinomas, and lymphomas are all examples of these disorders that fall under the umbrella of cutaneous oncology. Nail psoriasis, plaque psoriasis, pyoderma gangrenosum, and amyloidosis are just few of the inflammatory skin disorders that have responded well to intralesional MTX. It's also been shown to be effective in treating cutaneous infections, such as viral warts (11).

It was found by Hamdino et al. (2022)8 that the MTX group had more satisfied patients and needed fewer therapy sessions than the TrA group. A statistical analysis revealed, however, that this difference between the two groups was not substantive.

Although MTX's precise method of action remains unclear, it is known to lower intracellular decreased folate concentrations by inhibiting the enzyme di-hydrofolate reductase. This reduction, when provided at high dosage, inhibits purine and pyrimidine metabolism and, by extension, nucleic acid synthesis, producing antineoplastic actions. The accumulation of adenosine, a mediator of several of MTX's anti-inflammatory activities, is the result. When released into the extracellular space, adenosine has a number of anti-inflammatory effects, including preventing the accumulation of white blood cells, decreasing production of inflammatory cytokines like tumour necrosis factor alpha and interferon gamma, and dampening a wide range of monocyte, macrophage, and T-cell activities (12).

In a study published in 2020, Muhaidat et al.13 investigated the safety and effectiveness of two intralesional TrA concentrations, 5 mg/mL and 10 mg/mL, for the treatment of scalp areas with patchy AA. There was no discernible difference in response rates between the two groups, according to the findings.

After 12 weeks of intralesional TrA injection (5 mg/mL) at 4-week intervals, Ganjoo and Thappa (2013)14 found that 100% hair regrowth was obtained in 47% of patients. Similarly, Kuldeep et al. (2011)15 found that following 12 weeks of intralesional TrA injection (10 mg/mL) at 3-week intervals, 60% of patients saw hair regrowth (>75% of the affected area). There was no statistically significant difference between the MTX and TrA groups at the end of the 6-month treatment period, although the MTX group did better on the regrowth scale than the TrA group during the 3-month follow-up.

Vitamin D3 administered locally

Several research have looked at the effectiveness of topical vitamin D3 mimics in treating AA, which raises questions about the usage of vitamin D3 itself. For instance, Kim et al. (2012)16 reported full hair regrowth after therapy with topical calcipotriol for a resistant

case of AA. With calcipotriol, Narang et al. (2017)17 found a remarkable response rate of 59.1 percent in patients with AA. However, a research by Cerman et al. (2015)18 found that topical calcipotriol had only moderate success in treating AA.

Lower levels of VDR have been seen in serum and tissue samples from people with AA (Daroach et al., 201819; Fawzi et al., 201620). In fact, one research found an inverse relationship between VDR levels in tissue and AA severity (Fawzi et al., 2016) 20. Decreased VDR expression in AA may be linked to diminished Wnt/-catenin signals, which are involved in the hair-growth cycle. Reduced VDR expression is associated with abnormal hair follicle cycling in AA (Gerkowicz et al., 2017) 21. Keratinocytes in both human and mouse hair follicles have been shown to have abundant 1,25-dihydroxyvitamin D3 receptors (VDRs). Impaired hair follicle development and epidermal differentiation have both been related to a lack of VDR expression (18).

In a study comparing the effectiveness of intralesional vitamin D3 with intralesional saline, Rashad et al. (2022)22 found a statistically significant difference in favour of the intralesional vitamin D3 group. Calcitriol may affect the immune system since the vitamin D receptor (VDR) is present on every immune cell. Vitamin D may affect how certain dendritic cell subtypes migrate and mature, as well as how many chemokines and cytokines they produce. This gives them an important immune-regulating and tolerogenic function (23).

Trichosopy

Trichoscopic results showed a statistically significant decline in both the MTX and TrA groups, as shown in a research by Hamdino et al. (2022). These improvements persisted until the 12-week sessions' conclusion and the subsequent one-, two-, and three-month follow-ups.

At the completion of intralesional MTX sessions and at 4, 8, and 12 weeks of follow-up, Abdelsalam et al. (2021)10 observed a statistically significant decrease in all trichoscopic results. Srivastava et al. (2017)24 found that following intralesional TrA therapy, hair regeneration improved significantly at all follow-up intervals. Regrowth scores and trichoscopic results that are diagnostic of the condition showed this improvement, pointing to its cumulative nature. New vellus hair development was found in the research by Ganjoo and Thappa (2013)14, and the removal of tapering hair was reported as an early response to intralesional TrA therapy by these authors as well (using trichoscopy).

Hyperpigmentation was reported by 45.0% of patients in the MTX group and 5.0% in the TrA group, according to a study by Hamdino et al. (2022.8). In other disorders except alopecia, fortunately, no systemic adverse effects were described after intradermal injection of MTX (25).

Furthermore, Rashad et al. (2022)22 found that trichoscopic observations linked with disease activity, such as black spots, tapering hairs, yellow dots, and damaged hairs, reduced following three months of therapy with intralesional vitamin D. On the other hand, positive indicators of recovery were seen, such as the appearance of terminal and short vellus hairs. Only two patients, or 6.7% of the total, showed any remaining evidence of disease activity.

Effects Unwanted

Muhaidat et al. (2020)13 found that intralesional TrA had very mild, local side effects. In both groups of patients exposed to varying amounts of TrA, skin shrinkage was the most often reported adverse effect. Srivastava et al. (2017)24 found the same thing, finding no major adverse effects of TrA. They found that atrophy occurred in 4.6% of instances, while telangiectasia occurred in 7.5% of cases. Kuldeep et al. (2011)15 also observed that atrophy occurred at the locations of TrA injections. Using trichoscopy, Ganjoo and Thappa (2013)14 found atrophy in 16% of patients and telangiectasia in 3%. These results are at odds with those of a research comparing the efficacy and safety of intralesional PRP and TrA for the treatment of AA by Balakrishnan et al. (2020)26. Patients in the TrA group in their trial did not report any adverse effects, including cutaneous atrophy, hypopigmentation, telangiectasia, or burning.

Adverse effects in the MTX and TrA groups were short-lived and resolved throughout the course of the follow-up period, as reported by Hamdino et al. (20228). When comparing the MTX and TrA groups, there was a statistically significant difference in terms of adverse events.

In addition, Rashad et al. (2022)22 found that the side effects seen by trial participants were minor and hardly noticeable, and that no patients had to stop therapy due to them. Sixty percent of patients in the intralesional vitamin D3 group and sixty percent of patients in the control group had minor acceptable discomfort during injection. In the intralesional vitamin D3 group, 33.3% of patients had pinpoint bleeding at the injection site, whereas 43.2% of patients in the control group did. In addition, four patients (13.3%) in the intralesional vitamin D3 group had a vasovagal episode.

Conclusion:

Our findings suggest that intralesional MTX and vitamin D3 may provide preferable therapeutic options to intralesional TrA for the treatment of localised AA in adults. Hair regrowth and the loss of AA-specific trichoscopic characteristics might both be detected at earlier stages thanks to trichoscopy's usefulness.

References

[1] Lee HH, Gwillim E, Patel KR, et al. Epidemiology of alopecia areata, ophiasis, totalis, and universalis: A systematic review and meta-analysis. Journal of the American Academy of Dermatology. 2020; 82(3): 675-682.

[2] Fukuyama M, Ito T and Ohyama M. Alopecia areata: Current understanding of the pathophysiology and update on therapeutic approaches, featuring the Japanese Dermatological Association guidelines. The Journal of dermatology. 2022; 49(1): 19-36.

[3] Phan K, Ramachandran V and Sebaratnam DF. Methotrexate for alopecia areata: A systematic review and meta-analysis. J Am Acad Dermatol. 2019; 80(1): 120-127.

[4] Otberg N. Systemic treatment for alopecia areata. Dermatologic therapy. 2011; 24(3): 320-325.

[5] Bhat YJ, Latif I, Malik R, et al. Vitamin D level in alopecia areata. Indian journal of dermatology. 2017; 62(4):407.

[6] Rajabi F, Drake LA, Senna MM, et al. Alopecia areata: a review of disease pathogenesis. Br J Dermatol. 2018; 179(5):1033–1048.

[7] Ustuner P, Balevi A and Özdemir M. Best dilution of the best corticosteroid for intralesional injection in the treatment of localized alopecia areata in adults. J Dermatolog Treat. 2017; 28(8): 753-761.

[8] Hamdino M, El-Barbary RA and Darwish HM. Intralesional methotrexate versus triamcinolone acetonide for localized alopecia areata treatment: A randomized clinical trial. Journal of Cosmetic Dermatology. 2022; 21(2): 707-715.

[9] Kumaresan M. Intralesional steroids for alopecia areata. Int J Trichology. 2010; 2(1): 63-65.

[10] Abdelsalam SS, Hamdino M and Darwish HM. Efficacy of intralesional methotrexate in the treatment of alopecia areata. The Scientific Journal of Al-Azhar Medical Faculty, Girls. 2021; 5(3): 549.

[11] Searle T, Ali FR, Al-Niaimi F. Intralesional methotrexate in dermatology: diverse indications and practical considerations. Dermatologic therapy. 2021; 34(1): e14404.

[12] Bedoui Y, Guillot X, Sélambarom J, et al. Methotrexate an old drug with new tricks. International journal of molecular sciences. 2019; 20(20):5023.

[13] Muhaidat JM, Al-Qarqaz F, Khader Y, et al. A retrospective comparative study of two concentrations of intralesional triamcinolone acetonide in the treatment of patchy alopecia areata on the scalp. Clinical, Cosmetic and Investigational Dermatology. 2020; 795-803.

[14] Ganjoo S and Thappa DM. Dermoscopic evaluation of therapeutic response to an intralesional corticosteroid in the treatment of alopecia areata. Indian J Dermatol Venereol Leprol. 2013; 79(3): 408-417.

[15] Kuldeep C, Singhal H, Khare AK, et al. Randomized comparison of topical betamethasone valerate foam, intralesional triamcinolone acetonide and tacrolimus ointment in management of localized alopecia areata. Int J Trichology. 2011; 3(1): 20-24.

[16] Kim DH, Lee JW, Kim IS, et al. Successful treatment of alopecia areata with topical calcipotriol. Ann Dermatol. 2012; 24: 341-344.

[17] Narang T, Daroach M and Kumaran MS. Efficacy and safety of topical calcipotriol in management of alopecia areata: a pilot study. Dermatol Ther. 2017; 30(3): e12464.

[18] Çerman AA, Solak SS, Altunay İ, et al. Topical calcipotriol therapy for mild-to-moderate alopecia areata: a retrospective study. J Drugs Dermatol. 2015; 14: 616-620.

[19] Daroach M, Narang T, Saikia UN, et al. Correlation of vitamin D and vitamin D receptor expression in patients with alopecia areata: a clinical paradigm. Int J Dermatol. 2018; 57: 217–222.

[20] Fawzi MM, Mahmoud SB, Ahmed SF, et al. Assessment of vitamin D receptors in alopecia areata and androgenetic alopecia. J Cosmet Dermatol. 2016; 15: 318–323.

[21] Gerkowicz A, Chyl-Surdacka K, Krasowska D, et al. The Role of Vitamin D in Non-Scarring Alopecia. Int J Mol Sci. 2017; 18(12): 2653.

[22] Rashad AF, Elgamal E and Fouda I. Intralesional vitamin D3 in treatment of alopecia areata: A randomized controlled clinical trial. Journal of Cosmetic Dermatology. 2022; 21(10):4617-22.

[23] Illescas-Montes R, Melguizo-Rodríguez L, Ruiz C, et al. Vitamin D and autoimmune diseases. Life Sci. 2019; 15(233): 116744.
[24] Srivastava S, Goyal S, Dhillon KS, et al. Dermoscopic evaluation of therapeutic response to intralesional triamcinolone acetonide in the treatment of Alopecia areata. Int J Advan Medic. 2017; 4: 1175-1183.
[25] Chakravdhanula U, Anbarasu K, Verma VK, et al. Clinical efficacy of platelet rich plasma in combination with methotrexate in chronic plaque psoriatic patients. Dermatologic Therapy. 2016; 29(6): 446-50.
[26] Balakrishnan A, Joy B, Thyvalappil A, et al. A Comparative Study of Therapeutic Response to Intralesional Injections of Platelet-Rich Plasma Versus Triamcinolone Acetonide in Alopecia Areata. Indian dermatology online journal. 2020; 11(6): 920–924.