Intradermal Delivery of Alopecia Therapeutics: Current State and Future Prospects

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BACKGROUND Mesotherapy, a technique of transdermal microinjections of specific preparations, is increasingly used in fields such as dermatology and specifically for alopecia treatment. Its popularity stems from its ability to deliver drugs in a targeted manner while minimizing systemic side effects.

OBJECTIVE To assess and review current knowledge regarding the use of mesotherapy to deliver alopecia medications and highlight future directions for research.

MATERIALS AND METHODS The authors used research databases including PubMed and Google Scholar to identify current literature on mesotherapy and alopecia. The following search terms were used among other terms: "Mesotherapy" or "Intradermal" AND "Alopecia".

RESULTS Recent studies are promising for the intradermal delivery of dutasteride and minoxidil in the treatment of androgenetic alopecia.

CONCLUSION Although limitations exist with dutasteride and minoxidil therapies, further research regarding the preparation, delivery, and maintenance of these drugs is warranted as mesotherapy could establish this technique as a safe, effective, and viable treatment option for androgenetic alopecia.

Mesotherapy, a localized injection technique developed in 1958 by French physician, Dr. Pistor,[1] is used in a variety of medical fields, including pain management, cosmetics, and alopecia treatment. Androgenetic alopecia (AGA) is the most common type of alopecia and affects up to 50% of men and women.[2] Currently, oral therapies such as low-dose oral minoxidil (LDOM) and 5-alpha-reductase inhibitors are widely used for AGA treatment; however, they may cause systemic side effects. Low-dose oral minoxidil can lead to dose-dependent hypertrichosis and other less common side effects such as headaches, tachycardia, insomnia, hypotension, and edema due to fluid retention.[3] Meanwhile, 5-alpha-reductase inhibitors may cause psychological and sexual adverse effects.[4] Mesotherapy offers a solution to these systemic side effects by directing the drug specifically to the hair follicle, potentially increasing its local bioavailability while minimizing systemic exposure. The use of mesotherapy for AGA treatment has been studied and is used in some clinics, although it is not approved by the US FDA. However, mesotherapy has its own potential adverse effects, including local erythema, pain, pruritus, headaches, edema, local hematoma, folliculitis, and in rare cases an inflammatory reaction, granulomatous reaction, koebnerization, fat necrosis, and possible paradoxical nonscarring alopecia.[5,6]

In this article, the authors address the current literature regarding the efficacy, safety, and limitations of current mesotherapy studies as well as the preparation methods, dosing, and treatment schedules of this technique for the treatment of AGA.

Methods

This review analyzed the efficacy of mesotherapy for alopecia, focusing on minoxidil and dutasteride mesotherapy for AGA. A literature search on PubMed and Google Scholar databases identified relevant studies published until September 2022, using search terms such as "mesotherapy," "alopecia," "androgenetic alopecia," "minoxidil," and "dutasteride." The reference lists of identified articles were screened for additional publications, yielding 220 articles on Google Scholar and 24 on PubMed.

Inclusion and Exclusion Criteria

Included studies met the following criteria[1]: original research articles,[2] randomized controlled trials (RCTs), prospective or retrospective analyses,[3] human subjects

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diagnosed with AGA,[4] treatment interventions involving mesotherapy, and[5] reporting at least 1 outcome measure related to hair growth, hair density, or patient satisfaction. Excluded studies were[1] review articles, case reports, or case series,[2] nonhuman studies, and[3] non-English language publications.

Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts based on inclusion and exclusion criteria. Discrepancies were resolved through discussion and consensus. Full texts of selected articles were assessed for eligibility, and data extraction was conducted, including study design, patient demographics, treatment interventions, control groups, treatment schedules, outcomes assessed, and results.

Current State

The use of intradermal injections of alopecia medications, including minoxidil, dutasteride, and nutrient-only mesotherapy, has been the subject of a number of studies, which are summarized (see **Supplemental Digital Content 1**, Table S1, http://links.lww.com/DSS/B294). Although the results are encouraging, demonstrating the potential for mesotherapy as an efficacious treatment strategy with a low risk of side effects, they have limitations that need to be considered. In this section, the authors discuss studies that have evaluated the efficacy and safety of dutasteride, minoxidil, and nutrient-only intradermal injections for the treatment of AGA.

Randomized Controlled Trials on Dutasteride Mesotherapy

There are 3 RCTs on dutasteride mesotherapy. A 12-week study with 7 treatment sessions (weekly for the first 4 weeks, then every 2 weeks for 4 weeks, and a final injection after 4 weeks) by Abdallah and colleagues[7] in 2009 compared intradermal injections of 0.05% dutasteride (with D-panthenol, biotin, and pyridoxine) in 14 men with AGA against 14 men with AGA who received injections of 0.9% saline. The study found a statistically significant increase in hair density in the treatment group compared with the control group ($p < .001$). However, the study and others involving dutasteride mesotherapy have limitations, including short duration and the mixing of dutasteride solution with other nutrients, which lack strong evidence to support their use in nondeficient patients.

A 20-week study with 9 treatment sessions (once per week for 4 weeks, once every 2 weeks for 1 month, and once per month for 3 months) by Sobhy and colleagues compared 3 patient groups in a total of 90 men with AGA. Group A received pure 0.005% dutasteride mesotherapy. Group B received dutasteride-containing mesotherapy (dutasteride.05% with dexpanthenol, biotin, and pyridoxine). Group C received 0.9% saline mesotherapy.[8] Hair shaft diameters were increased in groups A and B ($p = .005$). Group B showed an increase in anagen hairs compared with groups A and C ($p = .005$). A 16-week study with 11 treatment sessions by Moftah and colleagues[9] comparing dutasteride-containing mesotherapy (dutasteride 0.5 mg, biotin 20 mg, pyridoxine 200 mg, and D-panthenol 500 mg) in 86 women with AGA against 0.9% saline mesotherapy in 40 women with AGA found statistically significant increases in hair diameters and patient-rated appearance in the treatment group ($p < .05$ for both measures). Injections were administered once a week for 8 consecutive weeks, then twice every 2 weeks, and finally once after 4 weeks.

The above studies demonstrate considerable subjective and objective benefits of dutasteride mesotherapy in male and female patients with AGA. Best results were achieved at a dosing of 1 to 2 mL of 0.05% dutasteride, with all studies starting with weekly injections for the first month and varying schedules thereafter often going to fortnightly injections for the second month and then subsequent monthly injections. The mixtures were often preprepared by compounding pharmacies and side-effect profiles consisting of local pain, headache, pruritus, and ecchymosis, typically resolved within 24 hours. Notably, none of the studies reported sexual side effects in any of their patients and the study by Sobhy and colleagues demonstrated no significant differences in semen volume, sperm concentration, sperm motility, or sperm morphology between pure dutasteride mesotherapy, dutasteride-containing mesotherapy, and normal saline mesotherapy ($p = .833$).

As these studies demonstrate dutasteride mesotherapy to be more effective than normal saline mesotherapy, the next step is performing studies comparing dutasteride mesotherapy with oral dutasteride, which would provide crucial information regarding the relative efficacy and safety of dutasteride intradermal injections compared with oral therapy.

Randomized Controlled Trials on Minoxidil Mesotherapy

Two RCTs aimed to evaluate the safety and efficacy of minoxidil mesotherapy. A 10-week study with weekly treatments by Uzel and colleagues[10] comparing mesotherapy of 2 mL of 0.5% minoxidil against 2 mL of 0.9% saline in a total of 58 female patients with AGA found that hair density decreased in the control group and increased in the experimental group 6 weeks after the last injections; however, it was not statistically significant ($p = .054$). For self-assessment, 69.2% of patients from the experimental group and 37.5% of patients from the control group perceived an improvement in hair loss ($p = .028$). A 12-week study of 60 female patients with AGA by Azam and colleagues compared 2 mL of topical 2% minoxidil applied daily for 12 weeks (30 patients) against minoxidil 2% injected into the scalp (once weekly for 4 weeks and then once every 2 weeks for 8 weeks, 30 patients) and compared with 20 normal controls. The study demonstrated improvements in percent anagen, telogen, and vellus hairs in both the topical and mesotherapy minoxidil compared with the control; however, the changes were greater in the

mesotherapy group ($p < .01$).[11] These studies on minoxidil mesotherapy used 1 to 2 mL of either 0.5% or 2% minoxidil injections with similar schedules to that of dutasteride mentioned above. The study by Uzel and colleagues did not show hypertrichosis in their patients and reported self-limited pain, pruritus, and burning that was greater in the mesotherapy group ($p < .010$).

A limitation of current minoxidil mesotherapy studies is the lack of comparison with other forms of minoxidil administrations and concentrations, such as LDOM and topical minoxidil 5%, which has been demonstrated to be more effective than topical 2% minoxidil and is more commonly used today.[12]

Non-RCT Studies on Dutasteride and Minoxidil Mesotherapy

A prospective analysis of 6 patients (5 men and 1 woman) with AGA who received 1 mL of intradermal 0.01% dutasteride injections every 3 months for 6 months showed increased hair density, diameter, and appreciable hair growth per photography in all patients.[13] This analysis was promising but limited by the small sample size, lack of a control group, and short study duration. A recent retrospective study that aimed to assess adverse events and efficacy of dutasteride mesotherapy analyzed 541 patients treated with 0.01% dutasteride mesotherapy for at least 2 sessions and with at least a 6-month follow-up. The median treatment duration was 17 months, with a median of 4-month intervals between injections, and the most common frequency being every 3 months. A total of 86 patients received dutasteride mesotherapy without concomitant treatments and clinical improvement was observed in 71 patients (86.6%), with 33 of the patients (38%) demonstrating a marked improvement, defined as an improvement of 1 grade or more on the Ebling scale.[14] No serious or sexual side effects were reported. The study was severely limited in that 84.15% of the total 541 patients were on concomitant hair loss therapies such as oral dutasteride, oral minoxidil, and oral finasteride. Although they analyzed patients on dutasteride mesotherapy as a monotherapy, it was a smaller group (16% of the total subjects). For the remaining subjects, the study did not control for concomitant medications as confounders. This limits both the ability to assess efficacy and side-effect profile of intradermal dutasteride therapy. Nonetheless, this study represents one of the largest studies investigating the utility of dutasteride mesotherapy to date.

Randomized Controlled Trial Studies on Nutrient-Only Mesotherapy

Two RCTs have examined nutrient-only mesotherapy for AGA. Hunter and colleagues[15] compared topical minoxidil 5% (Group A) with nutrient mesotherapy (Group B) in 30 female patients. Results showed no significant differences between groups in hair density ($p = .27$), hair loss ($p = .056$), and Ludwig classification improvement ($p = .210$). However, patient satisfaction was significantly higher in Group B ($p = .001$), with a significant difference in the number of hair follicles ($p = .007$) but not in hair follicle diameter ($p = .10$).

Gajjar and colleagues[16] compared microneedling plus nutrient mesotherapy (Group A) with 5% minoxidil (Group B) in 49 male patients. Dermoscopic evaluation showed no significant differences between groups for most parameters, but a significant difference in hair shaft diameter variation at the first month ($p = .04$) favored Group A. TrichoScan evaluation revealed no significant differences between groups, and subjective evaluation showed similar mild to moderate improvement for both treatments.

These studies have limitations, such as lacking negative controls, small sample sizes, and short follow-up periods, resulting in limited evidence for nutrient-only mesotherapy in treating alopecia. Further research is required to fully comprehend the benefits and drawbacks of this approach.

Future Research

Current studies on minoxidil and dutasteride mesotherapy exhibit limitations such as small sample sizes, short follow-up times, and lack of assessment of hair diameter changes, an important AGA treatment success marker.[17] More research is needed to evaluate the efficacy and safety of intradermal therapy while addressing these limitations. Intradermal delivery through mesotherapy may be useful for other medications to limit systemic side effects and for other types of alopecia, warranting further investigation.

Proper preparation, delivery strategies, and patient selection are crucial to reducing mesotherapy risks. Table 1 highlights potential risk mitigation methods. The efficacy of mesotherapy should be compared with current AGA treatment strategies. In addition, studies should determine the best preparation, administration, and maintenance strategies. Sterile conditions are required for mixture compounding to prevent contamination. Appropriate solvents should be used to avoid vascular occlusion. Two patients developed non-scarring alopecia after dutasteride mesotherapy, potentially due to ethanol as a solvent.[6] The authors recommended safer solvents, such as dimethyl sulfoxide.[18]

The ideal concentration for intradermal dutasteride remains to be determined. Mesotherapy studies have used concentrations of 0.01% or 0.05% for dutasteride and 0.5% or 2% for minoxidil.[7,10,11] The ideal interval between injections also needs examination, with current studies varying from weeks to months. Dutasteride's half-life is approximately 5 weeks, so depending on local bioavailability, more frequent injections may be unnecessary. The average shelf-life of dutasteride compounds for mesotherapy should be considered when discussing injection intervals. Compounding pharmacies report a 45-day shelf-life for dutasteride and minoxidil. More studies on local bioavailability of mesotherapy will help determine optimal maintenance schedules. Long-duration studies are necessary because AGA therapy improvements typically occur over several months.

TABLE 1. Proposed Methods Toward Mitigating Risk of Adverse Events With Mesotherapy

Adverse Event	Prevention Strategy
Local side effects including pruritus, pain, and erythema	Injections with finer needles A quick and gentle insertion of the needle Applying ice to the area before and after injections* Applying a vibration device during injections
Local reaction or drug–drug interactions	Avoid using a mixture of drugs
Infection	Sterile preparation and administration techniques
Local hematoma	Do not recommend for patients with bleeding disorders and patients on anticoagulants
Vascular occlusion	Use of an appropriate solvent Appropriate depth of injection
Koebner phenomenon	Caution regarding use in patients with cicatricial alopecia (although a rare adverse event) More research on electroporation as a needle-less drug delivery technique is needed[19]

* Icing is used before injections of various preparations such as anesthetics or platelet-rich plasma and has not been demonstrated to decrease absorption of the injected medication.[20,21]

Conclusion

The current studies suggest that mesotherapy may be an effective treatment strategy for alopecia with a low risk of side effects but exhibit the limitations discussed. The optimal concentration, volume, and frequency of injections are yet to be determined. Larger, controlled studies are needed to establish the safety and efficacy of mesotherapy for AGA treatment because this treatment method may provide alternatives for those concerned about the side effects of systemic minoxidil and dutasteride therapy. An additional limitation of mesotherapy is cost, with each injection as well as longitudinally if therapy must be maintained.

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