

Beyond Minoxidil: Emerging Therapeutics Delivered through Microneedle Platforms for Alopecia

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ABSTRACT

Alopecia is a heterogeneous group of disorders, in which chronic hair loss can be caused by a variety of mechanisms including follicular miniaturization, immune derangements, inflammation, alteration of androgen action, oxidative stress or disruption of the follicular niche. Minoxidil is still used for the treatment of pattern hair loss but its efficacy varies between individuals, and takes a long time to work, and can present some local tolerability problems. There is the possibility of it being limited to follicular targets, which can further limit its effectiveness. The microneedle (MN) system is a minimally invasive method that can temporarily bypass the stratum corneum and enable therapeutic agents to penetrate into the viable epidermis and superficial dermis surrounding hair follicles. This review identifies novel alopecia therapies, in addition to the classic minoxidil therapy, that are delivered via MN platforms: localized anti-androgens (finasteride and dutasteride), prostaglandin-pathway modulators, PRP and growth-factor-based therapies, extracellular vesicles and exosomes, natural bioactives (curcumin), and regenerative pathway-targeting agents (Wnt/ β -catenin signaling). New methods and techniques involving nucleic acids and gene regulation are also discussed. Special focus is given to the enhancing of localized follicular delivery with regard to the improvement of MN geometry, material selection, localization of the payload, controlled release and integration of nanocarriers. Recent studies involving the development of powder-based MN formulations (with an example of finasteride) and dissolving MN formulations containing microsphere formulations of dutasteride, curcumin–zinc metal-organic-framework MN patches, and exosome delivery systems using MN formulations of stem-cell related therapeutics have been reported as proof-of-concept studies. The review also looks at MN-related evidence as opposed to those that are still under clinical testing or preclinical. The main issues to be addressed for translation are dose standardisation, scalp-specific insertion, payload stability, manufacturing, sterilization, long-term safety and regulatory requirements. The localized, controlled, follicle directed, regenerative and potentially personalized alopecia treatment therefore is a possibility with MN-based delivery.

Keywords: alopecia; androgenetic alopecia; microneedles; dutasteride; finasteride; exosomes; extracellular vesicles; follicular drug delivery

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1. INTRODUCTION

Alopecia is an umbrella term for a variety of conditions characterised by an excessive amount of hair loss, diminished hair production, miniaturization of hair follicles, inflammation or the complete destruction of the hair follicles. Of these, androgenetic alopecia (AGA) is the most common patterned form of hair loss, while alopecia areata (AA) is a nonscarring autoimmune disease with a relapsing nature. Scarring alopecias are different however, as the hair follicles may suffer permanent damage. The basic biology is very different in each of these diseases, so it is unlikely that any single drug or delivery system will work for all types of baldness. There are several therapeutic strategies, however, that address similar common biological targets, extending the anagen phase, decreasing androgen activity, re-establishing

communication between the dermal papilla and the epithelial cells, controlling inflammation, enhancing perifollicular vascular support and stimulating follicular stem-cell activity.^{1 2}

Alopecia does not only affect the way a man looks. Hair loss can impact quality of life and self-confidence and result in psychosocial issues such as anxiety, social withdrawal, or other psychosocial problems. Currently treatment is a combination of pharmacological, procedural, regenerative and surgical treatments, which may be quite extensive in some patients despite minimal visible hair loss.¹ AGA therapy is still a pharmacological treatment that involves the use of topical minoxidil and 5 α -reductase inhibitors, and in selected cases, platelet-rich plasma (PRP), microneedling, low-level light therapy, and

hair transplantation. Immunomodulatory drugs such as Janus kinase (JAK) inhibitors have brought new treatment options to AA.^{3 4}

But, providing effective treatment delivery to the scalp is still difficult. The SC is a tight, lipid-rich barrier that restricts the permeation of numerous hydrophilic compounds, macromolecules, nanoparticles and biologics. Just crossing this barrier is also not enough to guarantee penetration of the hair follicle. This is because a lot of the targets that are associated with hair growth are not distributed all over the skin, but are found in specific areas of the follicles such as bulge, the isthmus, outer root sheath, dermal sheath, and the dermal papilla.^{5 6}

Microneedles (MNs) are micron-sized projections that are intended to provide temporary channels through the stratum corneum. According to the structure, they may promote permeation of the skin, act as a reservoir or a direct delivery channel for the therapeutic agent. Solid, coated, hollow, dissolving, and hydrogel-forming MNs have been investigated. Among these, dissolving MNs have attracted particular interest because drugs can be incorporated into the needle matrix and released as the material dissolves or disintegrates after insertion.^[7 8 9 10] This approach is particularly relevant to alopecia because it allows localized delivery while limiting tissue disruption and can be designed to provide either rapid or sustained release.

Research on MN-assisted hair treatment has traditionally focused on improving minoxidil penetration. However, the potential of this platform extends well beyond minoxidil. Many emerging alopecia therapies have limitations such as poor aqueous solubility, inadequate skin permeability, rapid degradation, instability, unwanted systemic exposure, or short residence times. Combining MNs with nanocarriers, microspheres, hydrogels, or bioactive scaffolds may help overcome some of these limitations. Moreover, the controlled microinjury produced during MN insertion can activate wound-healing responses, vascular signaling, and regenerative pathways. This creates the possibility of combining the effects of MN-induced stimulation with localized therapeutic delivery rather than using MNs solely as passive drug-delivery devices.^{11 12}

Accordingly, this review takes a “beyond minoxidil” approach to MN-based alopecia therapy. Rather than considering MNs only as penetration enhancers for established drugs, it examines their potential for delivering anti-androgenic, immunomodulatory, regenerative, antioxidant, pathway-directed, and biologic therapies. Particular emphasis is placed on the strength and maturity of the available evidence, distinguishing findings demonstrated directly with MN-based alopecia treatments from therapeutic approaches that remain biologically promising but have yet to be validated using MN delivery.

2. HAIR FOLLICLE BIOLOGY AS A RATIONALE FOR LOCALIZED MICRONEEDLE DELIVERY

The hair follicle is a dynamic mini-organ that continuously moves through the anagen, catagen, and

telogen phases. Dermal papilla cells provide signals that influence epithelial cells, while hair follicle stem cells (HFSCs) within specialized niches supply progenitor cells during regeneration. In AGA, anagen is shortened, the ratio of terminal to vellus hairs decreases and susceptible follicles gradually miniaturize, which is regulated by several signaling pathways, such as Wnt/ β -catenin, Sonic Hedgehog, BMP, Notch, and TGF- β .^{13, 14} In the follicular microenvironment and with the interference in regenerative processes, androgen signalling, especially via dihydrotestosterone (DHT), can make an impact.

This latter aspect is pertinent to localized delivery to the follicle. If a topical product is applied to the scalp and not absorbed, but stays in the stratum corneum, then a higher concentration or repeated application of the drug may be necessary to obtain adequate follicular exposure. This could result in higher exposure to the local tissue and lower exposure of surrounding tissues. It is also thought that particulate formulations may be deposited in hair follicles, although particle size, surface properties, density of follicles, sebum production and status of the follicular opening will all influence whether the particles are deposited in the follicles.^{5 6}

There are a number of ways that MN systems can impact delivery. Temporary microchannels are formed as a result of insertion, allowing molecules to penetrate deeper layers of the skin. Other factors in the arrangement and length of the needles can influence where the payload is deposited. Furthermore, the insertion of a tissue injury can trigger wound-healing mechanisms including the production of cytokines, growth factors, angiogenic signals and the remodeling of extracellular matrix. This response is particularly relevant to regenerative approaches for alopecia because the MN device itself may contribute to the biological effect rather than functioning only as a drug-delivery tool.^{11 15}

Delivery depth, however, needs to be carefully controlled. Needles that penetrate too deeply may cause unnecessary pain, bleeding, inflammation, or infection, while shallow insertion may fail to reach the intended follicular region. Device design therefore needs to account for scalp anatomy, hair density, follicular orientation, and changes associated with the underlying disease. A dissolving MN patch designed to deliver a therapeutic payload is also unlikely to require the same needle dimensions or geometry as a clinical microneedling cartridge used primarily to induce a controlled injury.

3. MICRONEEDLE PLATFORMS RELEVANT TO ALOPECIA

Solid MNs are mainly used to create temporary microchannels in the skin, after which the drug formulation is applied to the treated area. They are mechanically strong and relatively easy to fabricate, but the actual dose reaching the target depends on how the formulation spreads and diffuses through the skin. Coated MNs carry the drug directly on the needle surface and can provide rapid deposition after insertion. Their main limitation is the relatively small amount of drug that can be loaded onto the needle surface. Hollow MNs contain

internal channels that allow liquid formulations to be delivered under controlled pressure. This gives greater control over dosing, although fabrication is more demanding and blockage of the narrow channels can be a practical concern.^{8 16}

Dissolving MNs have received particular attention for emerging alopecia therapies because the active ingredient can be incorporated directly into a water-soluble or biodegradable polymer matrix. Polyvinylpyrrolidone, hyaluronic acid, chondroitin sulfate, dextran, gelatin, silk-derived materials, and other polymers have been investigated for this purpose.^{9 17} Once inserted, the matrix dissolves or degrades and releases the incorporated payload. These systems also avoid the disposal of sharp MN waste and can be engineered to provide either relatively rapid or sustained drug release. Their suitability for sensitive biological payloads depends on the polymer, fabrication conditions, and formulation process.

Hydrogel-forming MNs provide a different approach. Once inserted, the polymeric needles absorb fluid and swell, thereby allowing a drug to be delivered from an attached reservoir to the skin.¹⁸ This configuration is useful for longer delivery times, but tends to have a greater formulation and manufacturing complexity as compared to dissolving MNs. Such systems may be modified to deliver anti-androgens, prostaglandin modulators, or peptide-based therapeutics, in a repeated, low dose fashion, as would occur in alopecia.

Additionally, MN systems may also be used in conjunction with nanoparticles, liposomes, nanoemulsions, microspheres or metal-organic frameworks. From this perspective, it can be considered a “macro-to-nano” delivery approach, in which the MN is responsible for delivering the drug to the skin, and the nanosize system is responsible for controlling the drug’s solubility, stability and localization in the follicles, as well as its release after penetrating the skin.

Table 1. Microneedle platforms and their applications in alopecia treatment.

MN platform	Primary mechanism	Potential alopecia use	Major limitation
Solid	Creates transient microchannels	Adjunctive delivery of topical drugs, PRP, growth-factor formulations	Dose depends on post-MN application; variable delivery
Coated	Rapid dissolution/release of surface payload	Low-dose potent molecules and biologics	Limited payload capacity
Hollow	Pressure-driven liquid delivery	Controlled dosing of solutions, biologics or nanosuspensions	Complex fabrication; clogging risk
Dissolving	Polymer matrix dissolves in skin	Dutasteride, exosomes, natural compounds, nanoparticles	Payload stability and mechanical strength must be balanced
Hydrogel-forming	Swelling forms a delivery conduit	Sustained delivery from a reservoir	More complex device architecture
Hybrid MN–nanocarrier	Microchannels + nanoscale targeting	Poorly soluble drugs, EVs, pathway modulators	Scale-up, characterization and regulatory complexity

4. WHY MOVE BEYOND MINOXIDIL?]

Minoxidil stimulates hair growth in some patients, but the effect is not always seen and treatment typically must be continued for it to have an effect. The formulation may also impact tolerability and adherence. Despite being a small molecule, minoxidil is not very water soluble and can cause irritation, dryness or contact dermatitis on the scalp in some individuals with topical preparations. Nanocarrier-based formulations have been investigated to improve follicular deposition, but a recent systematic review found that clinical evidence in humans

remains limited. Greater drug deposition in experimental models does not necessarily translate into better clinical outcomes.¹⁹

Another limitation is that AGA involves multiple biological processes rather than a single therapeutic target. Depending on the patient and disease state, androgen signaling, inflammation, oxidative stress, vascular changes, or impaired stem-cell activity may contribute to follicular dysfunction. A delivery platform that can accommodate agents with different or complementary mechanisms may therefore have broader potential than a single-agent topical formulation. Possible approaches include local 5 α -reductase inhibition to reduce DHT formation, prostaglandin modulation to influence follicular cycling, regenerative biologics to support dermal papilla signaling, antioxidants to counter oxidative stress, and pathway-directed agents aimed at activating HFSCs.²⁰

The purpose of MN technology is not necessarily to replace minoxidil. Its greater value may lie in delivering therapeutic agents that are poorly suited to conventional topical administration. Candidates are particularly relevant when localized exposure could provide a therapeutic benefit, systemic exposure is undesirable, or the therapeutic molecule is too large, unstable, or poorly permeable to cross intact skin effectively. This consideration is especially important for biologics and extracellular vesicles, for which passage through the intact stratum corneum is inherently limited.^{7 21}

5. EMERGING ANTI-ANDROGENIC THERAPEUTICS THROUGH MICRONEEDLES

5.1 Finasteride

Finasteride inhibits type II 5 α -reductase, thereby reducing the conversion of testosterone to DHT. Oral finasteride is effective for AGA, but because the drug enters systemic circulation, androgen-sensitive tissues are also exposed and systemic adverse effects can occur. Topical finasteride has therefore been investigated to focus the treatment on the scalp and reduce its systemic absorption. Topical formulations have been shown to decrease scalp levels of DHT as well as improve a variety of hair-related outcomes in studies, though formulation strength, dose, and systemic absorption are factors to consider.^{22 23}

Another method of localization of finasteride is via MN delivery. To overcome the conventional solid MN approaches with their dosage restrictions, a powder-carrying MN system was designed to be inserted into the microchannels to deliver the drug finasteride. This was important because the study showed it was possible to deliver finasteride into the skin with a patch-based system, and if the amount of the drug can be deposited near the target area, then it may not be necessary to carry a high drug load.²⁴

Studies should take more than the overall permeation of the skin. The plasma and scalp concentrations of the drug, amount of drug delivered to the follicle, local inhibition of DHT, changes in the hair density or diameter, and adverse effects of the treatment would be useful endpoints. It is important to recognize that while greater total skin penetration per se may not be the indication of successful follicular targeting, the goal is to deliver greater concentration of the drug around the follicular unit, not more transdermal absorption.²⁵

5.2 Dutasteride

Dutasteride is an inhibitor of both type I and type II 5 α -reductase, meaning that the drug is more effective than finasteride at inhibiting the formation of DHT. It is well studied in AGA, but is a long half-life and will reach systemic levels when administered orally. These properties make localized delivery an appealing route to minimize the ingestion of unnecessary drug systemically while keeping activity at the scalp.²⁶

A recent method is by use of a dissolving MN patch with microspheres loaded with dutasteride for extended treatment of AGA. The system is designed to be both dissolving MNs to penetrate the skin barrier and microspheres with long-lasting properties. The purpose is to keep the drug in the treatment area and decrease the frequency of dosage; this design also illustrates the different functions of various parts of a drug delivery system—the MN is the skin-penetrating component, and the microspheres are the components that regulate the release of the drug.²⁷

Localized dutasteride delivery could potentially provide longer residence at the scalp, lower systemic exposure, and less frequent application. However, these potential benefits still need to be established in well-designed human pharmacokinetic and pharmacodynamic studies. Given the potency and persistence of dutasteride, local tolerability alone would not be sufficient to establish safety. Development should also include measurements of plasma dutasteride, serum DHT, reproductive safety parameters, and long-term adverse events.²⁸

Table 2. Anti-androgenic agents and MN development priorities

Agent	Therapeutic rationale	MN evidence	Key development question
Finasteride	Type II 5 α -reductase inhibition; local DHT suppression	Powder-carrying MN demonstrated feasibility	Can follicular targeting reduce systemic exposure while maintaining clinical efficacy?
Dutasteride	Type I + II 5 α -reductase inhibition	Dissolving MN + sustained-release	What local dose and release duration

		microspheres reported	provide adequate DHT suppression without systemic accumulation?
Topical anti-androgen combinations	Potential multi-target suppression	Mostly formulation-stage evidence	Can combination payloads be co-localized without instability or dose escalation?

6. PROSTAGLANDIN-PATHWAY MODULATORS

Prostaglandins are involved in regulation of the hair cycle, with PGE2 and PGF2 α generally associated with hair-supportive effects and PGD2 linked to growth inhibition in AGA. This has led to interest in prostaglandin analogues such as bimatoprost and latanoprost, particularly for eyelash and eyebrow disorders, with increasing attention to their potential use in scalp hair loss.²⁹ Clinical evidence summarized in a 2023 systematic review and meta-analysis suggests improvements in hair length and density with topical prostaglandin analogues, although dose and treatment frequency remain insufficiently defined.²⁹ Recent literature has also identified broader alterations in PGD2, PGE2, PGF2 α , and PGI2 signaling as potential therapeutic targets in AGA.³⁰

For MN-based delivery, the main opportunity is to concentrate prostaglandin modulators around the follicular unit while reducing the need for repeated surface application. Dissolving MNs could form a localized depot for prostaglandin analogues, whereas receptor-selective modulators or agents affecting prostaglandin metabolism could provide more pathway-specific approaches. While these MN systems are useful in alopecia, there are less direct evidence available than the systems are based on finasteride or dutasteride, and hence they can be regarded as emerging applications.³¹

Formulation stability should also be considered as many lipid signaling molecules are susceptible to the environment and oxidation. Therefore, the development of protective packaging, antioxidant selection, low water content matrices, and stability testing are required. Assessment should not only be based on measurements of hair growth but should also involve local pharmacodynamic effects based on prostaglandins if applicable.³²

7. REGENERATIVE BIOLOGICS: PRP, GROWTH FACTORS AND PEPTIDES

7.1 Platelet-rich plasma

Platelet-rich plasma (PRP) is a combination of growth factors and signaling proteins which are released from activated platelets such as platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor- β , and epidermal growth factor. Besides directly promoting hair growth, these mediators also influence other processes such as angiogenesis, remodeling of the extracellular matrix and signaling to the dermal papilla, which may contribute to the wider biological role of PRP in AGA.³³

The clinical results of PRP preparations have been promising but variable, possibly due to the differences in preparation, platelet concentration, activation, treatment protocols, and assessment of the treatment outcomes. More recent studies have evaluated microneedle mediated topical PRP as an alternative to intradermal injection, with potential benefit also noted and significant heterogeneity and risk of bias.³² The delivery methods of MN and intradermal injection were compared in a randomized split-scalp study, where MN showed similar trichoscopic results and reduced self-reported pain, thus establishing its suitability as a delivery method.³⁴

One of the primary concerns of MN-assisted PRP is then not just the penetration of the treatment. More attention should be paid to the biological dose given to the scalp. To enhance the reproducibility, platelet concentration, growth factor content, release and storage should be characterized. The fact that the composition of a PRP is different for every patient makes the use of the therapy for treatment of patients a unique translation challenge as compared to a pharmaceutical product with a known and reproducible dose.

7.2 Recombinant growth factors and peptide therapeutics

Direct action within the follicular microenvironment requires the presence of growth factors and short bioactive peptides which are not necessarily delivered by the conventional topical route due to their size, enzymatic instability and lack of permeability. MNs can overcome the stratum corneum barrier and provide localized deposition near the follicle. Potential candidates include VEGF-related angiogenic factors, fibroblast growth factors, insulin-like growth factor-related pathways, keratinocyte growth factor, and peptides that modulate dermal papilla activity.^{14,35}

Their delivery, however, requires careful control because growth factors can produce different biological effects depending on concentration and exposure time. Excessive or poorly controlled exposure may also lead to unwanted responses. MN systems should therefore be designed to provide localized, low-dose release rather than producing high systemic concentrations. Incorporating these molecules into biodegradable nanoparticles or hydrogel-based domains could improve their stability and prolong their residence at the target site. At present, most evidence for these approaches in alopecia remains preclinical, and their biological rationale should therefore be distinguished from demonstrated clinical efficacy.³⁶

8. EXTRACELLULAR VESICLES AND EXOSOME-BASED THERAPY

Extracellular vesicle(EVs), including exosome-enriched preparations, are being investigated as cell-free regenerative therapies. Their cargo contains proteins, lipids, messenger RNAs, and microRNAs that can alter the behavior of recipient cells. In hair biology, EVs derived from mesenchymal stem cells or dermal papilla-related sources have been reported to affect Wnt/ β -catenin signaling, angiogenesis, inflammatory pathways, and follicular cell activity.³⁷

Clinical evidence is still limited and varies considerably between studies. It also is important to note the terminology, as sometimes “exosomes” used in the field do not refer to a monodisperse population of EVs but rather a mixture of various EV populations.³⁸ The 2025 and 2026 reviews both identified the need for standardized manufacturing, characterization, and controlled clinical studies.

In alopecia, MNs provide a convenient way to deliver EVs into the target tissue. Microneedle patches were commonly cited as one of the delivery methods in a 2025 scoping review of exosome delivery for hair loss, and a more recent preclinical study demonstrated exosome delivery via dissolving MNs, resulting in better hair-regeneration outcomes and sustained release in experimental models, when applied to the treatment of AGA.³⁹

The pairing of EVs and MNs also poses a challenging quality-control challenge. During the fabrication and storage of the therapeutic product, the vesicles must remain intact and exhibit the desired biological activity. The important attributes are size of the vesicle, concentration, surface markers, protein and RNA content, potency, sterility, endotoxin levels, residual processing agents and storage stability. These properties may be changed by drying, solvent exposure, mechanical forces and interactions with the MN polymer.

The future EV-MN systems could be based on certain disease mechanisms instead of a general hair stimulation. Enriching EVs with regenerative microRNAs might be directed towards dermal papilla cells while anti-inflammatory cargo would be more applicable to immune-mediated alopecia. This would eventually pave the way for more specific regenerative strategies, albeit with further preclinical and clinical testing still needed.

9. NATURAL BIOACTIVES AND MULTIFUNCTIONAL SMALL MOLECULES

Natural bioactives are of interest for MN-based delivery because several have antioxidant, anti-inflammatory, anti-apoptotic, or anti-androgenic properties but are limited by poor aqueous solubility and inadequate skin penetration. Curcumin comes as a good example. It may modulate oxidative and inflammatory processes and has been effective in experimental models of hair regeneration, but is poorly soluble in water and chemically unstable and has poor bioavailability making it difficult to deliver it topically. Curcumin comes as a good example. It may modulate oxidative and inflammatory processes and has been effective in experimental models of hair regeneration, but is poorly soluble in water and chemically unstable and has poor bioavailability making it difficult to deliver it topically.⁴⁰

One notable proof-of-concept study developed a curcumin-loaded zinc metal-organic framework (ZnMOF) incorporated into a γ -polyglutamic acid MN patch. The MNs created temporary pathways through the skin and delivered the ZnMOF particles to the intended depth, where they provided sustained release of curcumin and Zn^{2+} . In preclinical models, the formulation was associated with antioxidant, anti-apoptotic, and anti-androgenic effects, along with increases in follicular and vascular markers.⁴⁰ Rather than delivering free curcumin, this approach combined the barrier-bypassing function of MNs with a nanocarrier designed to improve drug performance.⁴¹

Other natural compounds, including polyphenols, flavonoids, botanical extracts, and lipid-derived molecules, could potentially be incorporated into similar systems, although the supporting evidence is less consistent. Botanical extracts present an additional challenge because their chemical composition can vary between batches, making it difficult to identify the components responsible for the therapeutic effect. For pharmaceutical development, a well-characterized molecule or standardized fraction would therefore offer greater control than an inadequately defined plant extract.⁴²

Natural bioactives may ultimately be more useful as components of combination MN systems than as substitutes for established therapies. An antioxidant, for instance, could be paired with a local anti-androgen or regenerative biologic to address different aspects of follicular dysfunction. Such combinations would need clear mechanistic justification and careful assessment of compatibility, release behavior, and stability of each payload.

10. PATHWAY-DIRECTED REGENERATIVE THERAPEUTICS

Hair regeneration depends on coordinated signaling within the follicular niche. Wnt/ β -catenin promotes anagen initiation and follicular regeneration, while BMP, TGF- β , and related pathways influence quiescence, regression, and fibrosis.¹³⁴³ These pathways have therefore become targets for compounds and peptides that aim to reactivate follicular programs or modify stem-cell behavior.

One approach targets CXXC5, a negative regulator of Wnt/ β -catenin signaling, using cell-penetrating peptides such as PTD-DBM. Other preclinical strategies include Wnt agonists, GSK-3 β inhibitors such as CHIR99021, and modulation of retinoid, Shh, or BMP signaling.^{43,44}

MNs could provide localized delivery of these agents, particularly when only low concentrations are required and systemic exposure is undesirable. However, manipulating regenerative pathways requires careful safety assessment because prolonged proliferative signaling could affect non-target tissues. Therefore, long-term molecular and histopathological evaluation should also be performed in addition to hair-growth measurement.⁴⁵

Another possible pathway directed agent is retinoic acid. Though it is experimental and must be directly formulated and clinically validated, its signaling could be used to help mediate local exposure and potentially decrease the degree of irritation of topical retinoids.⁴⁶

11. RNA, GENE-REGULATORY AND PRECISION THERAPEUTICS: THE NEXT FRONTIER

RNA-based therapeutics may be developed to regulate the expression of androgen receptors, inflammatory mediators, inhibitors of hair growth, and genes that promote hair regeneration in order to treat alopecia. Cargos that are possible are siRNA, mimics and inhibitors of micro RNA and mRNA. Despite these difficulties, their delivery has been a challenge due to the need to penetrate the skin barrier, resist nucleases, reach target cells, and escape from endosomes.⁴³

RNA could be directly deposited into viable skin to overcome the first of these obstacles, which can be addressed by MNs. Lipid or polymeric nanoparticles and extracellular vesicles could also provide protection of the cargo and enhance cellular uptake. Rather than just stimulating hair growth, possible applications are the suppression of disease related pathways in AGA or modification of inflammatory signaling in AA.⁴⁷

Gene regulation using CRISPR is further away from clinical use. Unlike conventional drug delivery, safety issues like off-target effects, immunogenicity, persistence and limited reversibility demands a lot more safety testing. Hence, RNA therapy with MN should be regarded as a future research tool, not a clinical therapy.⁴⁸

In the short term, there are benefits to transient RNA modulation over permanent gene editing. Dissolving MNs could be used for delivering short term siRNA or mRNA to a specific area of the scalp with minimal or no permanent genomic modifications. Evaluation of tissue distribution, gene knockdown/expression, duration of effect and local and systemic immune responses would be required for development.⁴⁹

12. COMBINATION AND MULTI-COMPONENT MICRONEEDLE SYSTEMS

Combination delivery is a possible advantage of MN systems due to the fact that alopecia is a disease in which multiple biological pathways are involved. For instance, a patch might be a blend of an anti-androgen to help suppress DHT, a regenerative factor and an antioxidant. That being said, additional components should support the overall formulation with a defined therapeutic benefit, not simply complicate the formulation.⁵⁰

This flexibility also enables the control of space and time. Different MN compartments could provide rapid and sustained release, while separate regions could deliver agents at different depths. Such designs may better accommodate follicular anatomy and reduce interactions between incompatible payloads.⁵¹

Evidence from clinical microneedling also shows why the effects of the device and the drug should be assessed separately. In a 2026 randomized trial involving women with mild-to-moderate AGA, 2% minoxidil combined with microneedling did not significantly differ from

minoxidil alone over 24 weeks at the tested treatment frequencies.⁵² This suggests that MN-induced microtrauma may add limited benefit when the drug already achieves adequate penetration.

The greater opportunity may therefore be with payloads that have substantial delivery barriers, such as PRP, finasteride, dutasteride, curcumin-based nanocarriers, and EVs. Future studies should compare matched doses with and without MN delivery and measure follicular deposition, systemic exposure, and pharmacodynamic effects alongside hair-growth outcomes.⁵³

13. CURRENT EVIDENCE: PRECLINICAL VERSUS CLINICAL TRANSLATION

Evidence maturity differs substantially across therapeutic classes. Conventional microneedling with topical minoxidil has the largest human evidence base, although these studies mainly assess microneedling as a procedure rather than a drug-loaded MN product. Finasteride has direct proof-of-concept evidence using powder-carrying MNs, while dutasteride has progressed to dissolving MN patches incorporating sustained-release microspheres.²⁴ PRP also has clinical evidence for MN-mediated delivery, although its biological composition varies between preparations.²⁷

Exosome-based MN systems are developing rapidly, but clinical evidence remains limited. Engineered exosome-loaded dissolving MNs represent a more advanced regenerative approach, yet translation depends on consistent product definition, characterization, and validated potency assays.^{38,39} Similarly, natural-product systems such as curcumin-ZnMOF MNs address both formulation and skin-penetration challenges, but most efficacy data remain preclinical.⁴¹ Differences in hair cycling between rodents and humans further limit direct translation of animal findings.

For this reason, MN alopecia studies should clearly separate the level of evidence supporting each therapeutic approach: Level A, controlled human study using an MN-delivered therapeutic; Level B, human evidence for the therapeutic by another route combined with preclinical MN evidence; Level C, animal or ex vivo evidence using MN delivery; and Level D, mechanistic candidates without direct MN evidence. This framework helps prevent overinterpretation and makes clear which approaches still require clinical validation.⁵⁴

Table 3. Evidence maturity of emerging MN-enabled alopecia therapeutics

Therapeutic strategy	Direct MN evidence	Evidence context	Current development status
Finasteride	Yes	Preclinical/device study	Proof of concept; human pharmacokinetic and efficacy studies needed

Dutasteride	Yes	Dissolving MN + microspheres; preclinical	Promising long-acting concept; clinical translation needed
PRP	Yes	Human clinical studies	Procedural/biologic variability remains
Exosomes/EVs	Yes	Mostly preclinical/scoping clinical literature; emerging engineered MNs	High interest; standardization and controlled trials needed
Curcumin/natural bioactives	Yes	Preclinical MN studies	Formulation-focused; human efficacy not established
Prostaglandin analogues	Limited direct MN evidence	Human topical evidence + mechanistic rationale	Candidate for MN development
Wnt/pathway modulators	Early/preclinical	Mechanistic and animal evidence	High safety burden; exploratory
RNA/gene-regulatory cargo	Platform-level evidence	MN delivery established in other diseases; alopecia rationale emerging	Research frontier

14. FORMULATION AND DEVICE DESIGN CONSIDERATIONS

For pharmaceutical development, the key challenge is balancing MN strength, payload loading, release, and stability. A dissolving MN should be able to tolerate insertion in the scalp skin without rupturing and it should be slowly dissolved. Increasing the polymer content usually strengthens the polymer, but decreases its dissolution rate; increasing the water content usually increases dissolution rate, but decreases the polymer strength. Therefore, formulations should be tailored to the payload/needle geometry.¹⁷

There is also a large variation in therapeutic classes in terms of drug loading. Relatively small amounts of potent anti-androgens might be sufficient, while proteins and EVs may need higher amounts of anti-androgen to maintain biological activity. Biologics will need to be structurally stable during manufacture and storage, and frequently must be stabilized with a sugar, polyol,

surfactant or a protective polymer. Such excipients may, however, also have an effect on viscosity, mechanical properties or release.⁵⁵

Nanocarriers can make the separation of MN dissolution from drug release possible. Metal-organic frameworks and other systems have the potential to enhance delivery of poorly soluble compounds and lipid nanoparticles could be used to deliver RNA following the MN dissolution.⁵⁶

Another area of concern with the scalp application is that the dense hair may disrupt the contact of the patch and/or needle insertion. To this end, flexibility, adhesion and application force have to be optimized, ideally not only with animal skin models, but also with ex vivo human scalp models. The actual insertion depth and follicular deposition should be confirmed by imaging. Needle dimensions, mechanical strength, insertion efficiency, dissolution time, drug content, release profile, follicular deposition, microbial quality and stability are some critical quality attributes. Potency and structural integrity are critical for biologic loaded MNs as it is possible for a chemically stable formulation to have a biologically inactive or damaged biologic cargo.⁵⁷

15. SAFETY AND PATIENT ACCEPTABILITY

MN systems are not completely noninvasive, but minimally so. They can cause pinpoint bleeding, erythema, edema, irritation or discomfort depending on the length of the needle and its insertion force. **Generally**, at low risk, if proper hygiene is practiced, but there must be consistent microbial control if repeated application is made to the scalp. Too much mechanical stress can also cause inflammation that may be an issue in certain types of alopecia.⁵⁸

Assessment of safety for both the device and the payload must be carried out. Anti-androgens need systemic exposure to be monitored and for growth factors and pathway modulators, unwanted proliferation or activation of pathways must be monitored. Other issues associated with the immunogenicity, contaminants and manufacturing consistency are raised with EV-based systems. Impurities and batch-to-batch variations are also factors that need to be controlled in natural products.⁵⁹

The patient may find dissolving MNs more convenient to use as the needles will become blunter or dissolve after use, cutting down on sharps waste. Patch application may also be more time efficient

than topical application. The benefits of these should be shown with validated tools that measure pain, convenience, satisfaction and adherence—not just from the device design.⁶⁰

16. TRANSLATIONAL AND REGULATORY CHALLENGES

Translating MN-based alopecia products into clinical use requires more than demonstrating hair growth in animal models. A reproducible dose is essential, yet dosing in dissolving MNs can vary with polymer distribution, needle-to-needle differences, and incomplete insertion. Manufacturing must also be scalable, since laboratory micro-molding methods may not provide the dimensional consistency required for commercial production.⁶¹

Regulatory development can be more complex when a product combines a device with a drug or biologic. Both pharmaceutical quality attributes and device performance may need to be demonstrated. EV-loaded MNs add another layer of complexity because the active biologic may be regulated differently depending on the jurisdiction and intended use.⁶²

Clinical trials should also separate the effects of the MN from those of the payload. Appropriate comparators may include untreated or placebo MNs, topical free drug, MNs with vehicle, and drug-loaded MNs. Key outcomes should include hair density, terminal hair count, shaft diameter, standardized photography, patient-reported outcomes, and, where feasible, pharmacokinetic or pharmacodynamic measures.⁵²

Long-term follow-up is equally important because hair cycling occurs over months. Short animal studies or brief clinical trials may not establish durability. Extended monitoring should therefore assess persistence of benefit, cumulative irritation, pigmentary changes, scarring, and systemic exposure.

17. FUTURE PERSPECTIVES

Future MN research in alopecia is likely to focus less on simple penetration enhancement and more on programmable, disease-specific delivery. Combining MNs with nanocarriers could allow the device to control tissue access while the carrier manages cellular uptake and drug release. Stimulus-responsive materials may provide further control by releasing their payload in response to local signals such as pH, enzymes, reactive oxygen species, temperature, or light.⁶³

Personalized treatment could also benefit from digital imaging and computational tools. Trichoscopic measurements can track follicular density, miniaturization, and treatment response, while computational models may eventually help optimize dose and application frequency. More advanced closed-loop systems could combine sensing of local inflammatory or follicular signals with responsive drug release, although this remains largely conceptual.⁶⁴

Combination patches may be particularly relevant to regenerative therapy. A single MN system could incorporate an anti-androgen, EVs, and a regenerative small molecule, with each payload released according to a different schedule. Such designs could address several disease mechanisms simultaneously, but their additional formulation complexity would need clear justification.⁶⁵

Ultimately, MN development should be driven by a specific therapeutic need rather than device novelty. The strongest applications are likely to be those where conventional delivery results in poor follicular deposition, excessive systemic exposure, payload instability, poor adherence, or inadequate delivery of macromolecules. When a drug already reaches its target effectively, adding an MN may offer little benefit unless the resulting improvement is clinically meaningful.⁶⁶

18. CONCLUSION

Microneedle platforms provide a flexible way to provide novel therapies for alopecia outside of minoxidil. The primary benefit is their localized access to viable skin and the follicular microenvironment, which enables high levels of potent small molecules, biologics and nanoscale delivery vehicles to be delivered. There is a compelling rationale for local delivery of anti-androgen with the currently available finasteride and dutasteride MN systems, and for regenerative approaches with PRP and exosome based systems. The formulations of MN using curcumin also illustrate the potential for nanocarriers for overcoming poor solubility and limited skin penetration.

While these advances have been made, these are promising results in a pre-clinical setting and it should not be taken as a sign of clinical efficacy. There is a wide range of evidence from therapeutic classes, with many of the approaches still backed by only mechanistic or animal studies. Standardized dosing, follicular deposition and systemic exposure, long-term safety and well-controlled clinical trials should be the focus of future development. The aim should be for precise delivery and not just to penetrate the drug to the follicles: The therapeutic should get to the right follicular compartment, at the right dose, for the right length of time.

Then, there is the potential for MN technology to impact the treatment of alopecia as a more localized and controlled delivery, such as in the field of anti-androgenic therapy, regenerative signaling, natural bioactives and future RNA-based applications. The development of the devices will rely on a coordinated effort between various disciplines, including dermatology, pharmaceuticals, biomaterials, nanomedicine and regulatory science with clinical benefit being the main driver for the development.

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