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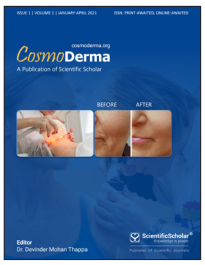

Editorial

Androgenetic alopecia – Update 2022

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Androgenetic alopecia (AA) is a common disease, affecting up to 80% of males and up to 40% of females during their lifetime. AA presents with different clinical picture and course among men and women. In addition to the well-known underlying mechanisms of AA, a new trigger emerged in recent years – COVID-19 disease (Gabrin's sign). Infection with SARS-CoV-2 increases the prevalence of AA in both men and women. Despite the fact that AA is not a life-threatening fatal disorder, it has a negative impact on self-esteem and other dimensions of quality of life.

AA has a number of comorbidities, which may be considered in further treatment developments. The most important include hormonal diseases and metabolic disorders (hyperandrogenemia, insulin resistance or polycystic ovary syndrome, and metabolic syndrome), cancers (thyroid, prostate, and testicular germ cell cells), cardiovascular disorders (hypertension and atherosclerosis), autoimmune diseases, and nutritional deficiencies.

FDA approved treatment options are 5-alfa-reductase inhibitors (finasteride and dutasteride – males only), topical minoxidil (for both genders), and hormonal treatment (females only). All of them have their own risk of adverse events and a limited efficacy.

Therefore, the good news is, new treatment options are on the horizon!

TOPICAL TREATMENT

Finasteride is an effective compound for male AA. The molecular weight is 372.54 g/mol. The molecule in its native form is used for oral application only. Oral finasteride and dutasteride have been associated with sexual dysfunction and neuropsychiatric complaints. To circumvent these problems, topical applications seem promising.

Since these molecules do not penetrate intact skin sufficiently, various techniques and technologies are under investigation. Microneedling is an established minimal invasive method to increase penetration of active compounds into deeper skin layers. Microneedling plus topical dutasteride improved the efficacy of topical application in a randomized, placebo-controlled study.

Another study investigated beta-sitosterol-loaded nanoparticles in combination with microneedling for AA. The authors used an animal model of testosterone-induced hair loss. The treatment was effective in reversal of androgen-induced hair loss and support of anagen hair growth phase.

A special formulation has been developed using aloe ferox gel, oregano oil for solubilization, and nanocubes to deliver the active compound. The particle size of the nanocubes ranged between 89 and 185 nm. Such a system would allow a topical treatment with finasteride with a better safety profile than oral treatment. Further studies are needed.

Another approach is the use of solid lipid nanoparticles decorated with chitosan as nanodrug carriers for finasteride. The mean particle diameter is 10.1 nm. This technology allows an extended drug release for 24 h. Chitosan supports drug retention within the skin.

Finasteride spray has been investigated in a randomized, double-blind, double dummy, parallel group, 24-week Phase III study in 323 male AA patients during 24 weeks of treatment. Final hair density was significantly higher compared to placebo. Since the systemic concentrations of finasteride were >10-fold lower than with oral drug, the risk of adverse events could be markedly reduced.

Prostaglandin F2-alfa analog bimatoprost has shown to stimulate growth of eyelashes in a 0.3% topical preparation. Subedi *et al*. (2002) aimed to improve skin penetration and efficacy in promotion of hair growth by a new topical formulation, containing both volatile and non-volatile solvents, spreading agent and antioxidants. This formulation coined BIM-T#5 significantly enhanced the human skin flux and deposition of the active compound in the dermis. In a mouse model with androgen-induced AA, BIM-T#5 stimulated hair growth, hair weight, and hair follicle density.

A formulation of bioactive peptides, vitamins, and trace elements supporting vascularity and hair follicle growth (QR678® and QR678 neo®) has been injected into scalp skin to treat female pattern AA in patients with polycystic ovary syndrome during eight sessions. These 20 patients suffered from Ludwig Grades I and II AA. After 1 year, more terminal hair with a larger hair shaft diameter was noted. In a second larger Phase-IV trial, 2428 male and female AA patients were treated with QR678 neo®. After eight sessions, hair density and terminal hair count increased.

Topical minoxidil is a prodrug that depends on sulfotransferase 1A1 (SUT1A1) in scalp skin to become active. Combining topical minoxidil with a topical SUT1A1 booster resulted in improved efficacy of minoxidil in male AA.

Cetirizine is an antihistamine that inhibits PGD2 and stimulated PGE2. The latter is involved in hair growth. A 1% topical cetirizine solution daily has been compared to placebo in 30 male AA patients. After 6 months, the cetirizine group showed a higher hair density, leading to improved patient satisfaction. Compared to 5% topical minoxidil, 1% cetirizine was less effective as shown in a randomized, single-blinded, and controlled study with 40 male AA patients over 16 weeks.

LASER AND PHOTODYNAMIC THERAPY

Low-level laser therapy (LLLT) has been discovered in 1967 by Endre Ester, but it took a long way to get acknowledged. A recent large-scale trial with a helmet-like device (iHelmet) analyzed 1383 adult patients with mild-to-moderate AA. The treatment was more effective in males than females, in patients with dandruff, rash, and pruritus and longer use of the device. Efficacy was not in about 50% of patients treated.

A clinical half-side study investigated topical minoxidil versus minoxidil and Capellux® LLLT in 21 males with AA. Treatment was performed twice a day for 6 months. Thereafter, combined treatment showed superior results for hair density.

In a pilot trial, photodynamic therapy with 5% 5-aminolevulinic acid in seven males with AA did not result in any improvement.

PLATELET-RICH PLASMA (PRP)

PRP has been used occasionally for AA patients but studies with larger patient numbers were missing. Qu *et al*. (2021) demonstrated the efficacy of PRP in mice and in a clinical trial in 52 male AA patients in a half-side application. The authors could verify upregulation of β-catenin, PDGF, and AKT signaling and repressed p53 signaling due to PRP injections. Mean hair count, hair density, hair shaft diameter, and anagen hair ratio improved at 6 months by PRP compared to control side.

Ozcan *et al*. (2022) compared PRP application by dermapen-mediated microneedling and point-by-point technique injection with a 30-gauge needle in 62 male AA patients, aged between 18 and 55 years. Three sessions were performed 2 weeks apart and a last session after 1 month. TrichoScan was used for objective assessment. Dermapen method was superior to multiple injections for hair density, anagen/telogen ratio, and hair length.

In a pilot study, PRP with the lower and higher platelet counts was compared. Higher platelet counts resulted in superior efficacy.

In a recent meta-analysis of published studies, longer and more frequent application of PRP in younger patients is capable to stimulate hair growth. Chemically modified PRP is better than inactivated and ≥2 centrifugations are better than a single centrifugation of PRP.

In a randomized trial in Chinese males with AA, electrodynamic microneedling was combined with 5% minoxidil topical solution versus topical minoxidil alone or microneedling alone. After 24 weeks, hair density was superior with the combination therapy. Analysis of scalp biopsies further demonstrated upregulation of frizzled class receptor 3, β-catenin, and lymphoid enhancer-binding factor 1 expression on mRNA and protein level. This argues for an activation of Wnt/β-catenin signaling pathway by the treatment approach.

ORAL TREATMENT

Conversion of testosterone to dihydrotestosterone is a major driver of AA. Inhibitors of the responsible enzyme

5-alfa-reductase, such as finasteride and dutasteride, are FDA approved for the treatment of AA in males. In a recent meta-analysis, both 5-alfa reductase inhibitors have been compared to each other. Dutasteride 0.5 mg/day was found to be more effective in stopping hair fall and increasing hair density in the frontal area and on vertex than 1 mg finasteride/day. Dutasteride had also a better safety profile.

Minoxidil as an oral drug has unwanted side effects such as hypertrichosis, edema, hypotension, and tachycardia. To reduce the risk of adverse events and to bypass hepatic first-pass metabolism, sublingual application seems to be attractive. In a prospective, randomized placebo-controlled, double-blinded dose-escalation Phase 1B, and clinical trial (HREC approval number 2017-09-669; ANZCTR number: ACTRN12618000606280), 40 males and females with AA were included in the study. Either sublingual minoxidil at a dosage of 0.45 mg daily or placebo was applied for 24 weeks. Twelve participants rolled into a 24-week open-label extension study and received minoxidil at higher dosage, that is, 1.35 or 4.05 mg daily. There was a dose-dependent increase of terminal hair density. The difference to placebo reached statistical significance. Treatment was well tolerated.

Conventionally, supplementation with minerals and vitamins is used to treat alopecia of various types including AA. A recent investigation analyzed 138 alopecia patients with supplementation of ferritin, zinc, Vitamin D, or thyroid-stimulating hormone. Comparing supplemented to non-supplemented patients did not reveal statistically significant changes in hair caliber or hair density due to supplementation. The limitation of this trial is the patient number. Theoretically, a larger number of patients could result in significant differences.

Oral setipiprant, a selective antagonist of PGD_2 receptor-2 and activation of eosinophils has been evaluated in a Phase 2a, randomized, double-blind, placebo-controlled (for setipiprant only), and multicenter study (ClinicalTrials.gov identifier NCT02781311) over 24 weeks of blinded treatment and 8 weeks of follow-up in male AA. The 3-armed trial compared 1 g setipiprant BID to 1 mg finasteride/day or placebo. The drug was safe, but the treatment did not show efficacy.

Janus kinase (JAK) inhibitors have been investigated for the treatment of severe alopecia areata in adults. Baricitinib – a JAK1 and JAK2 inhibitor – is the first FDA and EMA approved compound of its class for alopecia areata, a common autoimmune hair disorder. These drugs have a possible risk of thromboembolic events and infections including herpes zoster.

An upregulation of signal transducer and activator of transcription-3 gene in AA might provide a rational for the use of JAK inhibitors in AA but clinical studies are missing so far.

CONCLUSION

AA is a common disorder with a complex pathogenesis. Classical treatment has its limitations and safety issues. New ways of drug delivery and new compounds are on the horizon, but more clinical trials are needed.

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