GUIDELINE

Guidelines for the management of androgenetic alopecia (2010)

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OUTLINE OF GUIDELINES

Background and objectives
Androgenetic alopecia is a slowly progressive form of alopecia which begins after the onset of puberty. Although it is a physiological phenomenon, it may carry deep social implications for the affected individual due to the significant changes it can cause in the outward appearance of the patient.

In recent years, effective oral and topical medications have been developed for the management of androgenetic alopecia and are now used with increasing regularity in dermatological treatments. However, the fact remains that therapies with no scientific basis, and which, from the dermatological perspective, are entirely without effect, are still prevalent, with many patients unwittingly continuing to use these pointless therapies.

Under these circumstances, collecting scientifically based information with a view to developing guidelines to promote standardized treatments for androgenetic alopecia is a crucial matter for both physician and patient alike. While guidelines for the diagnosis and management of androgenetic alopecia have been developed and are available for use in Europe and the USA, these guidelines are less readily accepted in Japan due to differences in race, health care and social background. For this reason, we have undertaken the creation of a set of guidelines for the management of androgenetic alopecia adapted to the circumstances specific to Japan.

Process of preparing guidelines
The Guideline Planning Committee, consisting of androgenetic alopecia specialists, was established as a cooperative venture between the Japanese Dermatological Association and the Society for Hair Science Research (SHSR). A comprehensive list of therapies was drawn up by the committee and assessed using a set of clinical questions (CQ) designed for the purpose. The committee members were tasked with answering these questions through a study of published clinical research results. They then individually prepared their respective structured abstracts while taking various factors into consideration in order to determine the level of recommendation to be accorded to the treatments.

Positioning of guidelines
The guidelines were prepared as a tentative, standard regimen for management of androgenetic alopecia in Japan. Because it is important to provide optimal, individualized therapy for patients based on their background or clinical conditions, these guidelines were designed to assist in this endeavor. Therefore, it should be noted that physicians consulting these guidelines need neither to restrict their choice of therapy for individual patients nor limit their treatment policy in order to comply with the guidelines. It is unacceptable for the Guidelines Planning Committee to employ the guidelines in medical disputes or malpractice lawsuits, as such uses would significantly deviate from their original intent.

Funding and conflict of interest issues
The preparation of the guidelines was funded by a grant from the Japanese Dermatological Association. In cases where a member of the Guideline Preparation Committee was involved in the...
development of any relevant drug or therapy, he/she was barred from involvement in evaluating the said treatment recommendations. No other conflicts of interest were present among the members preparing the guidelines.

Collection of evidence
The following databases were used to prepare the guidelines: Medline, PubMed, SCIRUSSCOPUS, Japana Centra Revuo Medicina WEB, the Cochrane Database of Systematic Reviews, and papers accumulated by individual committee members. Relevant medical published work available in December 2009 was collected. Systematic reviews of randomized controlled trials (RCT) and each RCT paper were given priority as inclusion criteria. If these were not available, papers based on cohort and case-control studies were used. Case series studies were also consulted. Published work concerned with basic experiments or animal experiments was not included.

Criteria for determining evidence level and recommendation degree
Criteria for evidence level and recommendation degree used in the "Guidelines for the management of malignant skin cancer"1 were used in the present guidelines as shown below.

Level of evidence
I. Systematic review or meta-analysis.
II. One or more randomized controlled trials.
III. Controlled study without randomization.
IV. Analytical epidemiological study (cohort study or case-control study).
V. Descriptive study (case report or case series study).
VI. Opinions of an expert committee or individual expertise.

Grades of recommendation
A. Strongly recommended (on the basis of at least one level I or level II evidence corroborating the efficacy of the treatment).
B. Recommended (on the basis of at least one level II evidence of low quality, level III evidence of good quality or level evidence IV of extremely good quality corroborating the efficacy of treatment).
C1. May be considered for use, but not sufficiently corroborated (level III–IV evidence of low quality, multiple level V evidences of good quality or level VI evidence approved by the committee).
C2. Not recommended for use due to lack of evidence (there is either no evidence indicating efficacy or there is evidence indicating lack of efficacy).
D. Recommended to be avoided (superior quality evidence indicates either harmful effect or no effect at all).

It should be noted that the grade of recommendation specified in the text may not conform to the above-mentioned judgment criteria. The recommendation grade was determined by taking into account the evidence level, racial differences, insufficiency of evidence in some fields, the specific social circumstances in Japan and the utility of the guidelines themselves.

DISEASE CONCEPT, PATHOGENESIS AND DIAGNOSIS OF ANDROGENETIC ALOPECIA

Disease concept
The pathogenesis of androgenetic alopecia is characterized by a shortened anagen phase in the hair cycle and an increase in the number of hair follicles that remain in telogen. Clinically, hairs from the frontal area to the vertex of the scalp become thin and short velvus hairs, resulting in a receding frontal hairline and hair loss in the vertex.2–7 In contrast to telogen effluvium, pattern hair loss is a characteristic of androgenetic alopecia.

In Japanese male subjects, androgenetic alopecia occurs most significantly during the late 20s and 30s, gradually progressing to complete baldness after the forties. Unlike in men, hair loss patterns in women are observed in a relatively wide area of the vertex. The incidence of androgenetic alopecia in Japanese men of all ages, based on data collected 25 years ago, was the same as it is today, at approximately 30%. The incidence is approximately 10% among men in their 20s, 20% for those in their 30s, 30% for those in their 40s and approximately 40% for those in their 50s and older, thus clearly exhibiting an increasing trend with age.9 Although the onset and progression of androgenetic alopecia are associated with heredity and androgen,10 androgen receptor gene polymorphism on the X chromosome and disease-related genes on the autosomal chromosomes 3q26 or 20p11 have recently been identified as possible contributory genetic factors.11

Pathogenesis
Generally, androgen stimulates bone and muscle development and function while also promoting significant hair growth in areas such as the beard or chest hair. However, androgen also induces vellus hair transformation in the androgen-sensitive hair follicles of the frontal or vertex area. While androgen receptors are present in the dermal papilla cells of androgen-sensitive hair follicles, testosterone delivered to the dermal papilla cells of the hair follicles of the beard, frontal area and the vertex is converted to dihydrotestosterone (DHT), a much more potent androgen, via the action of type II 5α- reductase. DHT-bound androgen receptors induce growth factors or other similar factors in the beard, resulting in anagen prolongation. In contrast, DHT-bound androgen receptors in the androgen-sensitive hair follicles of the frontal or vertex area are reported to induce transforming growth factor-β or other factors which inhibit hair matrix cell proliferation, resulting in shortening of the anagen phase.12

Diagnosis
The diagnosis of androgenetic alopecia is based on the following considerations: progression of hair loss, family history of thinning and visual confirmation of a receding frontal hairline, and the presence of thin and short hairs in the frontal area and vertex. Use of a magnifying glass or dermoscopy may assist diagnosis. For the clinical classification of androgenetic alopecia, Ogata’s classification has been used in Japan9 and Norwood’s classification in Western countries.4 At present, a method of classification combining Norwood’s classification with the type II vertex in Takashima’s
classification is widely used in Japan. Diagnosis of androgenetic alopecia is relatively easy, but it is important to exclude chronic diffuse type alopecia areata, idiopathic chronic telogen effluvium, diffuse alopecia associated with systemic diseases such as collagen diseases and chronic thyroiditis, and the effect of general conditions such as anemia, crash diets, wasting disease, drugs and hormone replacement therapy.

**TREATMENT**

The treatment for androgenetic alopecia in Japan was evaluated using the following CQ. Published therapeutic procedures formulated with reference to the recommendation grade and comments for each CQ.

**CLINICAL QUESTIONS AND TREATMENT ALGORITHM**

Table 1 shows the clinical questions and the recommendation grades for each CQ. A treatment algorithm shown in Figure 1 was formulated with reference to the recommendation grade and comments for each CQ.

**COSMETIC MANAGEMENT**

At present there are no objective data indicating the therapeutic utility of wigs, hairpieces or toupees for androgenetic alopecia, nor are there any studies of the impact of prosthetics like wigs and other hairpieces on body image or quality of life of androgenetic alopecia patients. Such prosthetics are not considered a treatment per se for androgenetic alopecia, but may nonetheless serve the important purpose of ameliorating the appearance of patients, with the added benefit of not having any known side-effects. For this reason, the Guidelines Planning Committee does not discourage the use of wigs.

**REFERENCES**

CQ1  Is the topical application of minoxidil effective?

Grade of recommendation:  
CQ1.1 A for men  
CQ1.2 A for women  
Comments: Topical applications of 5% minoxidil should be used as a first-line topical treatment for men, and 1% minoxidil as a first-line topical treatment for women.

Description: Three 12-week randomized controlled trials with 2% minoxidil and 3% minoxidil performed in approximately 150 male patients followed by long-term administration (24 months) revealed that more than 1 year of treatment with 2% minoxidil and 3% minoxidil significantly promoted hair growth compared with the placebo group and induced no severe adverse reactions. Furthermore, two 12-week and 24-week randomized controlled trials with 2% minoxidil and 5% minoxidil demonstrated that 5% minoxidil significantly increased hair growth and volume compared with 2% minoxidil and induced no systemic adverse reaction. Moreover, 24-week randomized controlled trials with 1% minoxidil and 5% minoxidil performed on Japanese male patients showed a significant stimulatory effect on hair growth with the latter compared to the former, with no significant difference in the incidence of adverse reactions.

A 24-week randomized controlled trial performed on Japanese adult female androgenetic alopecia patients demonstrated significant hair growth with the use of 1% minoxidil compared to the placebo. Two 32-week randomized controlled trials were performed abroad on approximately 300 female patients, confirming the efficacy of 2% minoxidil.

Additionally, one non-randomized controlled trial focusing on adverse reactions resulting from a 1-year use of topical 2% minoxidil or a placebo in more than 20,000 male and female patients showed no significant difference in the incidence of adverse events. Because there is good evidence demonstrating the stimulatory effects of topical minoxidil on hair growth, 5% minoxidil is strongly recommended as a first-line treatment for men, and 1% minoxidil as a first-line treatment for women.

REFERENCES


CQ2  Is topical application of carpronium chloride effective?

Grade of recommendation:  
C1  
Comments: May be considered for use.

Description: A bilateral comparison study performed on androgenetic alopecia patients demonstrated the effect of 5% carpronium chloride on the promotion of alopecia in four out of six patients over a 1–6-month period relative to a placebo group. Two pre- and post-treatment studies demonstrated that the topical application of 10% and 5% carpronium chloride over a 2–6-month period promoted hair growth or suppressed alopecia progression in two out of four and three out of five patients, respectively. However, the number of patients in each clinical study was small, and consisted only of males. Additionally, the subjective methods used for judging the results did not allow statistical analysis, resulting in an evidence level equivalent to that of case reports. Thus, the studies failed to demonstrate a distinct hair growth effect.

However, a 12-week treatment of 30 androgenetic alopecia patients (without tabulation by sex) using Karoyan Apoecce (Daiichi-Sankyo Co., Ltd, Tokyo, Japan), which consists primarily of 1% carpronium chloride with added herbal medicines such as Kashu tincture and Chinuketsu ginseng tincture, showed a moderate or higher response in 20% of the patients and a slight response or higher in 60.0% of patients. Moreover, a 24-week topical hair treatment using solutions consisting of 2% carpronium chloride, the above herbal medicines, and hinoki-chioru in 86 androgenetic alopecia patients showed a moderate improvement rate of 26.7% in men, 54.5% in women, and a slight improvement rate of 89.3% in men and 90.9% in women. This is the only paper in which subjects were evaluated separately by sex.
Although the benefits of monotherapy with carpronium chloride have not been sufficiently demonstrated, we recommend its use on the basis of its proven utility in Japan, where it is often prepared in formulas containing herbal ingredients. (Carpronium chloride, a reverse carboxyl analogue of acetylcholine, has a vasodilatory effect.)

REFERENCES


CQ3.1 Is application of other topical reagents effective?

**Grade of recommendation:** C1

**Comments:** May be considered for use.

**Description:** There are two papers showing the efficacy of t-flavanone for the treatment of androgenetic alopecia. A bilateral study of a tonic containing either t-flavanone or a placebo was performed using 14 male subjects. A 6-month course of treatment increased the average diameter of hairs generally, while it increased the average diameter of new hairs specifically by approximately 20%, relative to pretreatment measurements. Furthermore, topical application of t-flavanone significantly decreased the number of shed hairs to 20% or less by the end of the 4–6-month treatment period, while the placebo did not show any change. A non-randomized controlled study using a tonic containing t-flavanone, a placebo, and a commercially available product was performed on 197 male subjects. This study showed improvement rates of 53.1% for the tonic containing t-flavanone, 34.8% for the commercially available one, and 20% for the placebo. Moreover, the first two groups showed an increase in the number of terminal hairs of 40 \(\mu\)m or more in diameter, whereas the placebo group showed a decrease in the number. All of the above-mentioned papers targeted male patients. There are as yet no reports examining effects on female subjects.

As shown above, only a small number of studies contain significant evidence demonstrating the stimulatory effects of t-flavanone on hair growth. Nonetheless, we recommend it on the basis of its having minimal side-effects. However, its benefits for female subjects remain unknown. (t-Flavanone is a synthetic compound derived from astilbin, an active component of *Hypericum perforatum* extracts.)

REFERENCES


CQ3.2 Adenosine

**Grade of recommendation:** C1

**Comments:** May be considered for use.

**Description:** Two papers have demonstrated the efficacy of adenosine for the treatment of androgenetic alopecia, one for male patients and the other for female patients.

In a non-randomized controlled trial using male subjects, 102 men received a 6-month, twice-daily topical application of a lotion containing adenosine or nicotinamide as a control. The results indicated a slight or higher improvement rate in 41 out of 52 patients (80.4%) in the adenosine-containing lotion group and in 16 out of 50 patients (32.0%) in the control group, demonstrating a significant difference between the two groups. In terms of hair diameter, the proportion of vellus hairs (<40 \(\mu\)m in diameter) decreased by several percentage points while the proportion of non-vellus hairs (>60 \(\mu\)m in diameter) increased by approximately 10% after a 6-month treatment regimen using adenosine-containing lotion.

In a double-blind study for female subjects, 30 women with female pattern alopecia received a 12-month, twice-daily topical application of adenosine-containing lotion or placebo lotion for 12 months. The effect was gauged by means of the physician’s subjective evaluation and interpretation of photographic evidence. The results indicated a mild or higher improvement in 11 out of 13 patients (85%) in the adenosine-containing lotion group and in five out of 14 patients (36%) in the placebo group, indicating statistically significant improvement in the former. No significant difference was observed between the two groups in the anagen hair rate, vellus hair rate and hair density. A significant increase was observed in the anagen hair rate and non-vellus hair rate (diameter of >80 \(\mu\)m) in the adenosine-containing lotion group at 6 and 12 months.
post-treatment. Additionally, self-evaluations by the subjects displayed rendered higher values in the adenosine-containing lotion group in terms of the increase in new hair growth at 12 months post-treatment, hair growth at 6 months post-treatment and suppression of hair loss at 6 and 12 months post-treatment.²

As mentioned above, although there is not much evidence demonstrating the stimulatory effect of adenosine on hair growth, we recommend it on the basis of its having minimal side-effects.

REFERENCES
1 Tajima M. Elucidation of “adenosine,” a novel hair stimulant. Anti-aging series 1 (Gray hair, alopecia, and hair growth). 2005; 100–103. (In Japanese.) (Level III).

Guidelines

CQ3.3 
Cytopurine/pentadecane
Grade of recommendation: C1
Comments: May be considered for use.
Description: Two papers have demonstrated the efficacy of cytopurine and pentadecane in the treatment of androgenetic alopecia.

In a double-blind study of cytopurine, 86 male subjects received a 16-week, twice-daily topical application of a solution containing 0.5% cytopurine (CTP) or 59% ethanol as a control. The results indicated that patients in the CTP group improved in terms of their “sparse terminal hair”, “vellus hair” and “scaling” ; what is more, there was a marked tendency for increased growth after 16 weeks as compared to after 8 weeks. In terms of the overall improvement rate, slight improvement was observed in two patients in the placebo group and in 12 patients in the CTP group, demonstrating a significant improvement in the CTP group (P < 0.01). The utility rating (taking into account the side-effects) was “slightly useful” or higher for three patients (7%) in the placebo group and 20 patients (47%) in the CTP group, showing a significantly higher value for the CTP group.¹

In a double-blind study of pentadecane, 150 men received a twice-daily topical application of a tonic containing 2.5% pentadecanoic acid glyceride (PDG) or ethanol as a control for 24 weeks. As a result, improvement rates (based on changes in the quantities of shed hair at the time of hair washing, the generation of vellus hairs and the change from vellus to terminal hair) were significantly higher in the PDG group than in the control group. Evaluation of both efficacy and adverse reactions showed a significantly higher utility rating for the PDG group (76.0%) in comparison to the control group (32%).² These results were obtained from male subjects only. As yet, there are no studies examining the efficacy in female subjects. Although there are some reports demonstrating hair growth effects due to cytopurine/pentadecane, the number of studies is insufficient. We recommend this treatment as a topical therapy on the basis of it having minimal side-effects. The utility of this agent for the treatment of female subjects is unknown. (Pentadecane is pentadecanoic acid glyceride and cytopurine [6-benzylaminopurine] is a synthetic cytokinin).

REFERENCES

CQ3.4 
Cepharanthine
Grade of recommendation: C2
Comments: Not recommended for use.
Description: Only one Japanese case report showed the efficacy of the topical application of cepharanthine for the treatment of androgenetic alopecia. This report claims that administration of topical cepharanthine to a 46-year-old male androgenetic alopecia patient receiving topical 5% minoxidil and oral 1% finasteride resulted in hair growth in the frontal area after 4 months.¹ The effects in female patients have not been investigated.

The benefit of topical cepharanthine has yet to be demonstrated. Hence, we do not recommend its clinical use until its efficacy is proven by clinical trials. (Cepharanthine is a bicoclaurin alkaloid derived from Stephania cepharantha.)

REFERENCES
Guidelines

CQ3.5 Ketoconazole
Grade of recommendation: C1
Comments: May be considered for use.
Description: While some studies conducted abroad report the efficacy of oral ketoconazole treatment, oral ketoconazole is not available in Japan. We will therefore evaluate the efficacy of topical ketoconazole application in this section.

Three reports examined the efficacy of topical ketoconazole in male patients with androgenetic alopecia. A pre- and post-treatment study of the daily topical application of a lotion containing 2% ketoconazole (KCZ) was performed using six androgenetic alopecia patients who washed their hair daily with the lotion for 10–12 months. A decrease in hair loss was observed in two patients based on evaluations by a dermatologist. Furthermore, a pre- and post-treatment study of the topical application of the 2% KCZ lotion twice-daily for 6 months conducted in 17 men with androgenetic alopecia showed a trend toward improvement based on evaluations by a dermatologist. Pull test results also significantly improved in these patients. Seventy-six percent of these patients demonstrated slight or higher improvement in hair growth, indicating the efficacy of this drug.

In a comparative study of 2% KCZ shampoo and a commercial shampoo (control) in 39 androgenetic alopecia patients, hair diameter (D μm) and anagen hair rate (A%) were measured to calculate the pilary index (PI) ([A%] × [D μm] = [PI]). Results showed that the PI value increased starting at 6 months post-treatment, and reached equilibrium at 15 months post-treatment, in the 2% KCZ group. In contrast, the PI values decreased gradually in the control group. All reported studies were conducted using male patients; no studies have been performed to examine the efficacy of KCZ in female patients.

As shown above, because there is some evidence regarding the efficacy of topical applications of ketoconazole on hair growth, we recommend its use as a topical therapy for male patients. However, its efficacy for female subjects is unknown.

REFERENCES

CQ4 Is oral administration of finasteride effective?

Grade of recommendation: CQ4.1 A for men
CQ4.2 D for women
Comments: It should be used as a first-line oral therapy in male patients and should not be used in female patients.
Description: Finasteride is an inhibitor of 5α-reductase type II, which converts testosterone into dihydrotestosterone (DHT). Eight good overseas randomized controlled trials,6–8 one good domestic randomized controlled trial13 and one non-randomized controlled trial11 performed using male patients aged 18 years or older. Thus, oral administration of finasteride should be limited to patients 20 years old or older in Japan, because its safety has not been established in younger patients.

The consensus among specialists overseas12 is that the drug should be used continuously for at least 6 months, and its effects evaluated after 12 months of continuous use. Discontinuation of oral treatment is known to result in the recurrence of symptoms.6

Side-effects recorded in a domestic clinical study over 1 year using 1 mg/day oral finasteride treatment showed a 2.9% incidence of sexual dysfunctions, such as erectile dysfunction, ejaculatory failure and decrease in ejaculate volume, demonstrating no significant difference from the placebo group.10 Importantly, patients rarely develop hepatic dysfunction although its frequency is unknown. For this reason, patients should be carefully monitored during treatment, which must be discontinued if hepatic abnormality is observed. Furthermore, in a randomized controlled trial,13 1 mg/day oral finasteride treatment over 48 weeks decreased serum prostate-specific antigen (PSA; a prostate cancer marker) levels by approximately 50%. When measuring serum PSA levels of a patient with androgenetic alopecia receiving finasteride therapy, a double-value evaluation should be made to screen for prostate cancer.

On the other hand, one good overseas randomized controlled trial confirmed that finasteride is ineffective in post-menopausal female androgenetic alopecia patients;14 thus, it is not approved for use in women. Furthermore, because finasteride treatment in pregnant women may affect the normal fetal development of male reproductive organs or other organs due to a decrease in DHT levels, it is...
contraindicated for use in pregnant women, women who may become pregnant or lactating women.

In general, because there is good evidence of the efficacy of oral finasteride on hair growth, we strongly recommend its use as a first-line drug for oral treatment of androgenetic alopecia in male patients. However, we do not advise its use in female patients given that it is ineffective in postmenopausal women and produces undesirable side-effects in fetuses.

REFERENCES


CQ5 Is hair transplantation useful?

Grade of recommendation: CQ5.1 B for autologous hair transplantation

Comments: Hair transplantation should be performed by experienced surgeons for the benefit of patients who have shown insufficient improvement after treatment with oral finasteride or topical minoxidil.

Description: Although there are no systematic reviews or randomized controlled trials on the benefits of autologous hair transplantation, there are annually 225 800 cases (86.2% in males and 13.2% in females) of transplantation of hair tissue from the occipital area to the affected areas.1 Beenhner has reviewed multiple previous reports which indicated that autologous hair transplantation has a graft survival rate of 82.5% or higher,2 a fact that corroborates its use as a standard form of treatment for alopecia.

Although the level of evidence regarding autologous hair transplantation is not remarkably high, the committee assigns this treatment a grade B recommendation only in the cases where it can be performed by a surgeon with sufficient experience and skill. Additionally, the treatment should be a last resort, in cases where oral finasteride treatment or topical application of minoxidil has had an insufficient effect. This decision was made after due assessment of the domestic and international precedents for this treatment and on the degree of the psychological distress caused to the patient by the condition.

Regarding prosthetic hair implantation using synthetic hairs, there have been many reports of adverse effects from this procedure.3 The US Food and Drug Administration bans the use of synthetic hair.4 However, the Ministry of Health, Labor and Welfare of Japan does not currently prohibit the use of synthetic hairs. The Medical Treatment Law in Japan will not be violated as long as the procedure is performed at an appropriate medical facility. There is little evidence that the benefits outweigh the risks of prosthetic hair implantation. There are adverse effects that cannot be overlooked, albeit not so serious as to merit inclusion in an evidence level. For these reasons, we currently do not advise the use of prosthetic hair implantation in routine medical practice. (The structured abstracts on CQ5 were not listed herein because there are no data constituting a high evidence level.)

REFERENCES

1 ISHRS Practice census 2007. Extrapolated number of hair restoration services. Title 21-Food and Drugs. 48 FR 25136, June 3, 1983 (Level VI).