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GUIDELINE

Guidelines for the diagnosis and treatment of male-pattern and female-pattern hair loss, 2017 version

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ABSTRACT

Male-pattern hair loss (MPHL, androgenetic alopecia) is a slowly progressive form of alopecia which begins after puberty. In 2010, we published the first Japanese edition of guidelines for the diagnosis and treatment of MPHL. It achieved the original goal of providing physicians and patients in Japan with evidence-based information for choosing efficacious and safe therapy for MPHL. Subsequently, new therapeutic drugs and treatment methods have been developed, and women's perception of MPHL has undergone change and the term "female-pattern hair loss (FPHL)" is becoming more common internationally. Thus, here we report a revised version of the 2010 guidelines aimed at both MPHL and FPHL. In these guidelines, finasteride 1 mg daily, dutasteride 0.5 mg daily and topical 5% minoxidil twice daily for MPHL, and topical 1% minoxidil twice daily for FPHL, are recommended as the first-line treatments. Self-hair transplantation, irradiation by light-emitting diodes and low-level lasers, and topical application of adenosine for MPHL are recommended, whereas prosthetic hair transplantation and oral administration of minoxidil should not be performed. Oral administration of finasteride or dutasteride are contraindicated for FPHL. In addition, we have evaluated the effectiveness of topical application of carpronium chloride, *t*-flavanone, cytopurine, pentadecane and ketoconazole, and wearing a wig. Unapproved topical application of bimatoprost and latanoprost, and emerging hair regeneration treatments have also been addressed. We believe that the revised guidelines will improve further the diagnostic and treatment standards for MPHL add FPHL in Japan.

Key words: androgenetic alopecia, evidence-based medicine, female pattern baldness, guideline, review.

OUTLINE OF GUIDELINES

Background and objectives

Male-pattern hair loss (MPHL) or androgenetic alopecia is a type of alopecia that begins after puberty and progresses gradually. Although alopecia is a physiological phenomenon, it has a considerable impact on the quality of life (QOL) because it greatly affects aesthetics. In recent years, effective oral and topical medications have been developed for the management of MPHL and are now used with increasing regularity in dermatological treatments. However, the fact remains that therapies with

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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.

The first version of the guidelines (2010) achieved the original goal of improving the diagnostic and therapeutic standards for MPHL in Japan and provided information based on scientific evidence to both physicians and patients.

Subsequently, new therapeutic drugs and treatment methods were developed, and women's perception of pattern hair loss underwent change. This has led to the revision of the guidelines. Unapproved hair regeneration treatments have also drawn much social attention. We will also address this issue.

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Process of preparing the guidelines

The drafting of the "Japanese Dermatological Association's guidelines for the management of androgenetic alopecia 2010" was undertaken as a joint project by the Japanese Dermatological Association and Society for Hair Science Research (SHSR), and they were made public by the Japanese Dermatological Association in 2010. The same SHSR members, with expertise in the area of hair disorders, who were involved in the drafting, were selected as core members for revising the guidelines. The members of the drafting committee were approved by the Japanese Dermatological Association before starting the revision process. This revision process is a project of the Japanese Dermatological Association. In the meetings, the selection/addition of clinical questions (CQ) selected in the first edition was first discussed, and the division of roles was decided. Each member of the committee collected evidence in the area for which they were responsible, including that from the first edition and onwards, drafted a structured abstract and wrote the text on the grades of recommendations. We attempted to form a consensus of opinion through a number of meetings and put together the drafting committee's collective view. Finally, the revised guidelines were evaluated by the representatives of the Japanese Dermatological Association.

Collection of evidence

The databases used were Medline, PubMed, SCI-RUSSCOPUS, Japan Medical Abstracts Society Web and the Cochrane Database of Systematic Reviews, as well as articles collected by individual members. We collected published work that was searchable on the databases until December 2016. The selection criteria were set to prioritize systematic reviews of randomized controlled trials (RCT) and individual articles on RCT. We also referred to non-RCT and case series, when we were unable to collect evidence of such high standards. Published work on fundamental studies and animal studies was excluded.

Criteria for determining levels of evidence and grades of recommendations

Classification of the levels of evidence and the grades of recommendations were based on the classification standards set forth in the "Guidelines for the diagnosis and treatment of cutaneous malignancy, second edition" by the Japanese Dermatological Association.[1]

1 Levels of evidence:

- I Systematic reviews/meta-analyses.
- II One or more RCT.
- III Non-RCT.
- IV Analytical epidemiological studies (cohort studies and case–control studies).
- V Descriptive studies (case reports and case series).
- VI Opinions of expert committees and experts.

2 Grades of recommendations:

- A Strongly recommended (at least one body of level I evidence that indicates efficacy or high-quality level II evidence).
- B Recommended (at least one body of poor-quality level II evidence that indicates validity or high-quality level III evidence, or level IV evidence of excellent quality).
- C1 Permissible (poor-quality level III to IV evidence, multiple bodies of high-quality level V or committee-approved level VI evidence).
- C2 Not recommended (no evidence that indicates validity or evidence that indicates invalidity).
- D Strongly not recommended (high-quality evidence that indicates invalidity or harmfulness).

It should be noted that the grades of recommendations that appear in this article may not necessarily conform to the above-mentioned criteria. The reason for this is because the grades of recommendations for some of the items were determined based on the consensus of the committee, considering that the evidence in this field is lacking on an international scale, the historical background and special circumstances of Japan, and the practicality of the guidelines for management.

Funders and conflict of interest

The research funding of the Committee for the drafting of the Japanese Dermatological Association's guidelines was used to cover the expenses required for drafting this set of guidelines. The committee members involved in the development of a specific drug or treatment were excluded from directly involving themselves in the determination of the grade of recommendation. With the exception of such cases, the committee member involved in the drafting of the guidelines had no declared conflict of interest.

Disclosure method

This set of guidelines is to be made public on the Japanese Dermatological Association's website and published in the *Journal of Dermatology*.

Revision of guidelines

This set of guidelines is in the second edition. We intend to make future revisions regularly.

Disclaimer

This set of guidelines describes the present medical standards based on objective facts from the standpoint of clinical dermatologists. The guidelines should be applied flexibly to individual cases, and they are not intended to limit the discretionary power of a physician and his/her treatment strategy. Therefore, using this set of guidelines in a medical dispute or medical litigation is a grave deviation from the original purpose, and the committee for drafting guidelines finds it unacceptable.

Treatments and drugs that are not permitted under health-care services provided by health insurance and their grades of recommendations are described in this set of guidelines, provided that there is medical evidence from Japan or overseas. A portion of the guidelines also describes use outside the scope of health insurance. This is because guidelines are a description based on medical evidence, and they should not be a manual for health-care services under health insurance. However, approval from medical institutions and informed consent from the patient or family must be obtained before providing treatments or administrating drugs that are outside the scope of health insurance.

DISEASE CONCEPT, PATHOGENESIS, DIAGNOSIS AND TREATMENT

Disease concept

An increased number of hair follicles that remain in the telogen phase, as a result of the shortened anagen phase due to repeated hair cycles, is the basis of the pathogenesis of MPHL. Clinically, hairs from the frontal area to the vertex of the scalp become thin and short vellus hairs, resulting in a receding frontal hairline and hair loss in the vertex, and ultimately disappears from the skin surface.[2–7] This clinical condition is the same between men and women, and patterned hair loss is one of its characteristics unlike telogen effluvium.

In Japanese male subjects, the mean incidence across all ages was approximately 30%.[8] The incidence increases with age at approximately 10%, 20%, 30% and less than 40% for those in their 20s, 30s, 40s and 50s, respectively.[9] Although the onset and progression of MPHL are associated with heredity and androgen,[10] androgen receptor gene polymorphism on the X chromosome and disease-related genes on the autosomal chromosomes 17q21 and 20p11[11] have recently been identified as possible contributory genetic factors.

In contrast, unlike in men, hair loss is observed in women as a pattern wherein the hair in a relatively large area of the vertex becomes scarce. The time of onset also differs from men, and the incidence increases in the climacteric period.[12] Furthermore, there are cases where their pathogenesis cannot be explained by androgen dependency.[13] The use of the term "female-pattern hair loss" (FPHL) is becoming more common internationally rather than androgenetic alopecia in women. In view of such differences in pathogenesis, we decided to use the term FPHL in this set of guidelines for diagnosis and treatment.

Pathogenesis

Generally, androgens stimulate the development of bones and muscles, and also promote significant hair growth in areas such as the beard or chest hair. However, androgens also induce vellus hair transformation in the androgen-sensitive hair follicles in the frontal area or vertex. 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, through 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

Table 1. Summary of clinical questions (CQ)

No.	Clinical questions	Grades of recommendations
CQ1	Is oral administration of finasteride effective?	A (MPHL) D (FPHL)
CQ2	Is oral administration of dutasteride effective?	A (MPHL) D (FPHL)
CQ3	Is topical application of minoxidil effective?	A
CQ4	Is hair transplantation effective?	Self-hair transplantation B (MPHL) C1 (FPHL) D for prosthetic hair transplantation
CQ5	Is irradiation by LED and low-level lasers effective?	B
CQ6	Is topical application of adenosine effective?	B (MPHL)) C1 (FPHL)
CQ7	Is topical application of carpronium chloride effective?	C1
CQ8	Is topical application of *t*-flavanone effective?	C1
CQ9	Is topical application of cytopurine and pentadecane effective?	C1
CQ10	Is topical application of ketoconazole effective?	C1
CQ11	Is wearing a wig effective?	C1
CQ12	Is topical application of bimatoprost and latanoprost effective?	C2
CQ13	Is introduction of growth factors and cell transplantation therapy effective?	C2
CQ14	Is oral administration of minoxidil effective?	D

FPHL, female-pattern hair loss; LED, light-emitting diode; MHPL, male-pattern hair loss.

frontal or vertex area are reported to induce transforming growth factor-β and Dickkopf-1 which inhibit hair matrix cell proliferation, resulting in shortening of the anagen phase.[14]

Diagnosis

Diagnosis of MPHL consists of interviewing the patients regarding their family history and time course of hair loss and confirming visually of a receding frontal hairline, and the presence of thin and short hairs in the frontal area and vertex. A magnifying glass or dermoscopy is used to assist diagnosis. For the clinical classification of MPHL, Ogata's classification has been used in Japan[9] 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 *et al.*'s classification[8] is widely used in Japan. The Ludwig classification has been used for the classification of FPHL, but diagnostic criteria that consider early diagnosis and differential diagnosis have been proposed.[15,16]

Diagnosis of MPHL is relatively easy, but it is important to exclude chronic diffuse type alopecia areata. In FPHL, it is also important to exclude 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

Treatments of MPHL in Japan are examined using the following CQ (Table 1). As references, treatment protocols and guidelines published overseas on MPHL are listed.[2,3,5,6]

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CQ1: IS ORAL ADMINISTRATION OF FINASTERIDE EFFECTIVE?

Grade of recommendation: A (MPHL), D (FPHL).

Recommendation: Oral administration of finasteride is strongly recommended for individuals with MPHL, but it should not be administrated for individuals with FPHL.

Commentary: Finasteride inhibits 5α-reductase type 2, which converts testosterone to its more active form, DHT.[17] With regard to the efficacy of oral finasteride, one systematic review and 12 RCT on MPHL, and one RCT on FPHL have been conducted.[17–29] With regard to MPHL, in a systematic review that analyzed 12 RCT involving 3927 male subjects with an observation period of 12–24 months or longer, the number of terminal hairs per 1-cm^2 area of hair loss significantly increased in the finasteride administration group compared with the placebo group after both 6 months ($P < 0.001$) and 24 months ($P < 0.001$) of administration.[29] The relative risk of sexual dysfunction in the finasteride administration group was also reported to be 1.39 (95% confidence interval [CI], 0.66–1.95) and tended to be elevated in comparison with the placebo group.[29]

Moreover, in an RCT that examined the effects of finasteride (1 mg daily, 0.2 mg daily) in 414 Japanese male subjects for an observation period of 48 weeks, photographic effect evaluation of the crown showed that administration of 1 mg finasteride daily produced a moderate or better improvement in 58% of the subjects, whereas the administration of 0.2 mg finasteride daily produced a moderate or better improvement in 54% of the subjects.[26] In a non-RCT that continued the administration of 1 mg finasteride daily, the improvement rate increased. Moderate or better improvement was observed in 68% and 78% of the subjects after continued oral administration for 2 and 3 years, respectively.[27]

In another observational study with 801 Japanese male subjects, photographic effect evaluation showed that continued oral administration of finasteride (1 mg daily) for 5 years produced an improvement in 99.4% of the subjects.[28] The effect was more prominent in subjects younger than 40 years and in those with less severe cases.

Moreover, in an observational study that examined the effects of finasteride (1 mg daily) in 27 male subjects for an

observation period of 6 months, improvement was observed in both the visual analog scale (VAS) and Dermatology Life Quality Index (DLQI), which are indicators of the QOL of patients. VAS improved from 21.4 to 44.8 ($P < 0.0001$) and DLQI improved from 5.74 to 3.40 ($P < 0.01$).[30]

In a non-RCT on finasteride (1 mg daily) involving 374 Japanese male subjects, with an observation period of 2 years, that was conducted subsequent to an RCT on finasteride (1 mg daily, 0.2 mg daily) involving 414 Japanese male subjects, with an observation period of 48 weeks, no adverse reaction associated with sexual function was found in patients who transitioned from a daily dose of 0.2 to 1 mg and from placebo to a daily dose of 1 mg, whereas one case each of gastric ulcer and colon polyp, whose causal relation was unknown, was observed in patients that transitioned from placebo to a daily dose of 1 mg.[27] Although its incidence is unknown, hepatic dysfunction may occur on rare occasions as a significant adverse reaction. Moreover, in an RCT on finasteride (1 mg daily) involving 355 male subjects with an observation period of 48 weeks,[31] levels of serum prostate-specific antigen (PSA), a prostate cancer marker, decreased by approximately 50%. Therefore, the serum PSA levels should be doubled when diagnosing prostate cancer in a patient with MPHL on finasteride. Subsequently, with regard to FPHL, in an RCT on finasteride (1 mg daily) involving 137 female subjects with an observation period of 1 year, the number of terminal hairs per 1 cm^2 decreased in both the finasteride administration (−8.7) and placebo groups (−6.6), and no significant difference was found between the finasteride administration and placebo groups.[32] Similar to dutasteride, finasteride may also affect the normal development of reproductive organs in male fetuses, due to decreased DHT levels when administrated to pregnant women. Therefore, administration of finasteride to pregnant women or women suspected to be pregnant and lactating women is contraindicated.

As described above, there is high-level evidence regarding hair growth effect of orally administrated finasteride on MPHL; thus, oral administration of finasteride is strongly recommended. Conversely, oral administration of finasteride is not recommended for FPHL.

However, while clinical trials overseas established its safety in men aged 18 years or older, clinical trials in Japan did not establish its safety in men younger than 20 years. Oral administration should also be continued for at least 6 months or more to confirm its effect.[25] Its effect is lost once oral administration is discontinued.

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CQ2: IS ORAL ADMINISTRATION OF DUTASTERIDE EFFECTIVE?

Grade of recommendation: A (MPHL), D (FPHL).

Recommendation: Oral administration of dutasteride is strongly recommended for MPHL. Conversely, it is contraindicated for FPHL.

Commentary: Dutasteride inhibits both 5α-reductase types 1 and 2, which convert testosterone to its more active form, DHT.[33] With regard to the efficacy of orally administrated dutasteride on MPHL, one meta-analysis,[34] three RCT[33,35,36] and one non-RCT[37] have been conducted. No clinical trials have been conducted on the effects of dutasteride on FPHL.

In a systematic review[34] involving 4950 male subjects with an observation period of 6–60 months that analyzed 16 RCT, the percentage of subjects whose hair volume increased based on photographic hair evaluation was compared. The group that was orally administrated 0.5 mg dutasteride daily showed better effects than the placebo group (odds ratio, 16.38; 95% CI, 9.32–33.29).

In an international RCT that included Japan, which has the largest number of cases, involving 917 male subjects with an observation period of 6 months where 0.5 mg dutasteride and 1 mg finasteride daily were used, dutasteride also showed better effects in terms of increasing the total number of hairs and hair diameter, but no significant difference was found between the two groups in the number of terminal hairs that were 60 μm or wider in diameter. Furthermore, 7-point scoring ranging from marked exacerbation (−3) to marked improvement (+3) was conducted to photographically evaluate the crown and forehead, and although no significant difference in the scoring was found between the two groups, dutasteride showed better effects in an evaluation by three members of the expert panel of the clinical trial. However, the score difference was small, with 0.14 and 0.24 on the forehead and crown, respectively. Therefore, further investigation is required to elucidate the difference in their effects.

In a non-RCT conducted in Japan involving 120 male subjects, with an observation period of 52 weeks, where 0.5 mg of dutasteride daily was used,[37] the number of non-vellus hairs, number of terminal hairs and diameter of non-vellus hairs increased by 13.5/cm^2, 15.2/cm^2 and 6.5 nm, respectively, at 52 weeks. In a photographic evaluation (7-point scoring) of the crown by three dermatologists on the panel, hair volume significantly increased by 1.34 and 1.50 from baseline at 26 and 52 weeks, respectively. However, whether a significant improvement was found between weeks 26 and 52 was unclear.

With regard to the adverse reactions of dutasteride, in the aforementioned international clinical trial[36] and a Korean post-marketing surveillance study with 712 cases,[38] the incidence of adverse events was 3.3%, 5.4% and 3.3%, and 1.3%, 1% and 0.1% for reduced libido, impotence and ejaculatory dysfunction, respectively. Meanwhile, in the aforementioned non-RCT[37] conducted in Japan (120 cases, 52 weeks), the incidence was relatively high at 8.3%, 11.7% and 5.0% for reduced libido, impotence and ejaculatory dysfunction, respectively.[37] So far, one must carefully read the description on the attached document, when administrating dutasteride, provide sufficient explanation regarding the adverse reactions, including sexual dysfunction, and obtain consent. Serum PSA levels should also be doubled when diagnosing prostate cancer in a patient with MPHL on dutasteride.[39] Moreover, similar to finasteride, dutasteride may also affect the normal development of reproductive organs in male fetuses due to decreased DHT when administrated to pregnant women. Therefore, administration of dutasteride to women is contraindicated.

As described above, there is high-level evidence regarding the hair growth effect of orally administrated dutasteride on MPHL; thus, oral administration of dutasteride is strongly recommended. Conversely, oral administration of dutasteride is not recommended for FPHL.

However, its safety is not established for Japanese men younger than 20 years because only one international clinical trial was conducted with male subjects aged 20 years or older. Moreover, in the aforementioned clinical trial, the effects of long-term administration exceeding 1 year and changes in hair volume after discontinuation of administration were not investigated.

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CQ3: IS TOPICAL APPLICATION OF MINOXIDIL EFFECTIVE?

Grade of recommendation: A.

Recommendation: Topical application of minoxidil is strongly recommended (MPHL, 5% minoxidil; FPHL, 1% minoxidil).

Commentary: With regard to the efficacy of minoxidil, 14 RCT[40–53] and one systematic review[54] on MPHL, and 10 RCT[55–64] and one systematic review[65] on FPHL have been conducted.

First, with regard to MPHL, in a systematic review[54] involving 924 male subjects with an observation period of 24 weeks that analyzed five RCT[40–44] using a 2% minoxidil solution, the total number of hairs in the area of hair loss significantly increased, with a mean of 20.90 (95% CI, 9.07–32.74) in the 2% minoxidil group compared with the placebo group.

Two RCT compared 2% and 5% minoxidil solutions.[48,49] In one of these RCT with a larger number of male subjects and an observation period of 48 weeks, the increase from baseline in the number of non-vellus hairs per 1 cm^2 of the hair loss area was a mean of 3.9, 12.7 and 18.6 hair strands in the placebo, 2% minoxidil and 5% minoxidil groups, respectively. A significant increase was found in the 5% minoxidil group compared with the other two groups (vs placebo, $P < 0.001$; vs 2% solution, $P = 0.025$).[49]

Foam-type minoxidil is also used outside Japan.[50–52] In an RCT involving the largest number of male subjects (352 subjects) with an observation period of 16 weeks who used foam-

type 5% minoxidil, a significant increase ($P < 0.0001$) from baseline in the number of hairs per 1 cm^2 of the hair loss area with a mean of 4.7 and 20.9 hair strands in the placebo and foam-type 5% minoxidil groups, respectively.[50]

In Japan, an RCT involving 300 male subjects, with an observation period of 24 weeks, which compared 1% and 5% minoxidil solutions,[53] was conducted. The mean increase in the number of non-vellus hairs in a 1-cm^2 area of hair loss from baseline in the 1% minoxidil group was 21.2 hair strands, whereas a significant increase ($P = 0.02$) of a mean of 26.4 hair strands was found in the 5% minoxidil group.

Subsequently, with regard to FPHL, a systematic review involving 1242 female subjects, with an observation period of 24–32 weeks, that analyzed eight RCT using 1%, 2% and 5% minoxidil showed the efficacy of minoxidil.[65] In the minoxidil group, the number of hairs in a 1-cm^2 area of hair loss increased by a mean of 13.18 (95% CI, 10.92–15.44) compared with the placebo group. With regard to adverse events, the results of an analysis of four RCT with 725 subjects showed that the relative risk was 1.12 (95% CI, 0.61–2.06), 1.24 (95% CI, 0.82–1.87) and 2.05 (95% CI, 0.96–4.37) for the 1%, 2% and 5% minoxidil groups, respectively.[65]

In a systematic review involving 631 female subjects with an observation period of 26–52 weeks that analyzed three RCT on 2% and 5% minoxidil, the total number of hairs in a 1-cm^2 area of hair loss was smaller with a mean of 2.12 (95% CI, 5.47–1.23) in the 2% minoxidil group than the 5% minoxidil group, but no significant difference was found between the two groups.[65] With regard to adverse events, the results of an analysis of four RCT with 1006 subjects also showed that the relative risk was 1.02 (95% CI, 0.91–1.20), and no significant difference was found between the two groups.[65] However, evidence quality of these analyses on the increase in the number of hairs and adverse events is low, and further investigation is required.

No clinical trials using a 2% minoxidil solution have been conducted in Japan, but a randomized clinical trial, involving 280 female subjects, with an observation period of 24 weeks, using a 1% minoxidil solution, has been conducted. The increase in the number of non-vellus hairs in a 1-cm^2 area of hair loss from baseline was a mean of 2.03 and 8.15 in the placebo and 1% minoxidil groups, respectively. Thus, the 1% minoxidil group showed significant ($P < 0.001$) hair growth promotion effect compared with the placebo group.[63]

Itching, erythema, desquamation, folliculitis, contact dermatitis and facial hirsutism in both men and women have been reported as adverse events caused by minoxidil. In an RCT involving 393 male subjects with an observation period of 48 weeks comparing 2% and 5% minoxidil solutions,[49] the incidence of dermatological symptoms, such as itching and contact dermatitis, in the 5% minoxidil group (6%) was higher than that in the 2% minoxidil (2%) and placebo groups (3%).

Furthermore, in an RCT involving 381 female subjects, with an observation period of 48 weeks, where 2% minoxidil (twice a day) and 5% minoxidil (twice a day) were used, the incidence of dermatological symptoms in the 5% minoxidil group (14%) was higher than that in the 2% minoxidil (6%) and placebo groups (4%).[61] In contrast, in an RCT involving 113 female subjects with an observation period of 24 weeks, the incidence of dermatological symptoms in the 5% minoxidil group (once a day) was significantly lower ($P = 0.046$) than that in the 2% minoxidil group (twice a day).[64] Hence, there is no consensus on the adverse events caused by the two solutions.

Very few ingredient patch tests for adverse events of topical minoxidil have been performed. In the aforementioned RCT involving 393 male subjects, only three of 10 subjects who presented with symptoms of contact dermatitis caused by 5% minoxidil underwent a patch test, and two of them tested positive for propylene glycol, a solvent of the minoxidil solution.[49] As such, adverse events of topical minoxidil may not be caused by minoxidil alone. On the other hand, telogen effluvium during the early stages of using topical minoxidil has been reported. Providing explanation of this possibility to the patients is necessary because this may lead to discontinuation of topical application.[66]

As described above, there is high-level evidence regarding the hair growth effects of the topical application of minoxidil Thus, topical 5% and 1% minoxidil for MPHL and FPHL, respectively, are strongly recommended.

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CQ4: IS HAIR TRANSPLANTATION EFFECTIVE?

Grade of recommendation: B (MPHL) and C1 (FPHL) for self-hair transplantation, and D for prosthetic hair transplantation.

Recommendation: Self-hair transplantation is strongly recommended for MPHL. Self-hair transplantation is permissible for FPHL. Conversely, prosthetic hair transplantation is not recommended for MPHL and FPHL.

Commentary: No systematic reviews or RCT have been conducted on the efficacy of self-hair transplantation. However, 397 048 patients (men, 84.7%; women, 15.3%) underwent self-hair transplantation worldwide in 2015.[67] Beehner also evaluated a number of studies in his/her book and reported that self-hair transplantations had a high survival rate of more than 82.5%.[68]

In contrast, adverse events caused by prosthetic hair transplantation have been reported in many previous studies.[69] The US Food and Drug Administration has indicated prosthetic hair fibers as harmful devices and practically banned its use.[70]

A case series on the efficacy of prosthetic hair transplantation has also been conducted. In a cases series involving 133 subjects with an observation period of 3 years, where prosthetic hair fibers (Biofibre®; Medicap, Carpi, Italy) were used.[71] The fiber loss was of more than 10% per year in 91.4% of the cases, 15% in 7.8% of the cases and 20% in 0.8% of the cases. However, little evidence suggests that the benefits would eventually outweigh the risks for long-term observation.

As described above, in light of the vast body of clinical results both domestic and overseas, self-hair transplantation is recommended for MPHL and permissible for FPHL, in cases where oral administration of finasteride and dutasteride or topical minoxidil is ineffective, and if no other options are available, provided that the transplantation is performed by a physician with sufficient experience and skills. Nevertheless, although no issues exist regarding the Medical Service Act for performing prosthetic hair transplantation in Japan, we cannot overlook the incidence of adverse events and, as a general rule, prosthetic hair transplantation should not be performed until high-level evidence on its safety has been obtained.

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CQ5: IS IRRADIATION BY LIGHT-EMITTING DIODES AND LOW-LEVEL LASERS EFFECTIVE?

Grade of recommendation: B.

Recommendation: Irradiation by light-emitting diodes (LED) and low-level lasers is recommended.

Commentary: With regard to the efficacy of irradiation by LED and low-level lasers, four RCT[72–75] and one non-RCT[76] on MPHL, and three RCT[74,75,77] on FPHL have been conducted.

First, with regard to MPHL, in an RCT involving 110 male subjects, with an observation period of 26 weeks, where a low-level 655-nm laser (irradiation thrice a week) was used,[72] the number of hairs increased by 19.8/cm^2 in the low-level laser irradiation group compared with that before irradiation, and decreased by 7.6/cm^2 in the control group (control red light source). Four cases of mild paresthesia and four cases of mild urticaria were also observed as adverse reactions of laser irradiation.

Second, with regard to FPHL, in an RCT involving 122 female subjects, for an observation period of 26 weeks, that used a nine-beam laser irradiation device (655 nm) and 12-beam laser irradiation device (six beam, 635 nm; six beam, 655 nm),[74] the number of anagen hairs significantly increased in women by 20.2/cm^2 (control group, 2.8/cm^2) and 20.6/cm^2 (control group, 3.0/cm^2) in the nine- and 12-beam laser irradiation groups, respectively. The number of hairs also significantly increased in the male laser irradiation group. Adverse reactions caused by laser irradiation included dryness (5.1%), itching (2.5%), tenderness (1.3%), tingling sensation (1.3%) and thermal sensation (1.3%) of the irradiated skin.

As described above, with regard to the hair growth effects of LED and low-level lasers, sufficient evidence supports their efficacy, and their adverse reactions are relatively mild. Therefore, use of appropriate instruments is recommended when performing irradiation by LED and low-level lasers.

However, the aforementioned instruments have not been approved in Japan, and the type, wavelength and output of the light source vary by report.

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CQ6: IS TOPICAL ADENOSINE EFFECTIVE?

Grade of recommendation: B (MPHL), C1 (FPHL).

Recommendation: Topical adenosine is recommended for MPHL and is permissible for FPHL.

Commentary: With regard to the efficacy of adenosine, three RCT on MPHL and one RCT on FPHL have been conducted. First, with respect to MPHL, in an RCT on MPHL involving 101 male subjects, with an observation period of 6 months, where a 0.75% adenosine-containing lotion was used, the number of those that experienced moderate or better improvement in hair diameter, vellus hair ratio and thick hair ratio was 41 of 51 subjects (80.4%) in the adenosine-containing lotion group and 16 of 50 (32.0%) in the control group.[78]

In an RCT involving 38 male subjects, with an observation period of 6 months, where a 0.75% adenosine-containing lotion was also used, the number of vellus hairs thinner than 40 μm in diameter significantly decreased ($P = 0.0154$), the number of thick hairs equal to or thicker than 60 μm in diameter significantly increased ($P < 0.0001$) and hair density significantly increased ($P = 0.0470$) in the adenosine-containing lotion group compared with the control group.[79]

Moreover, in an RCT involving 94 male subjects, with an observation period of 6 months, where a 0.75% adenosine-containing lotion and 5% minoxidil lotion were used, no significant difference was found in the thick hair ratio in the affected area between the two groups, suggesting that the efficacy of 0.75% adenosine-containing lotion, which is commercially available as a therapeutic agent for MPHL, is similar to 5% minoxidil lotion.[80]

Second, with respect to FPHL, in an RCT involving 30 female subjects, with an observation period of 12 months, who used a 0.75% adenosine-containing lotion, a significant improvement was found in the growth rate of anagen hair and thick hair ratio in the adenosine-containing lotion group compared with the placebo group. In the adenosine-containing lotion group, 11 of 13 subjects (85%) experienced a moderate or better improvement, whereas five of 14 subjects (36%) in the placebo group experienced a mild or better improvement. The growth rate of anagen hair and the ratio of thick hair equal to or thicker than 80 μm in diameter significantly increased at 6 and 12 months, after use in the adenosine-containing lotion group.[81]

As described above, there is sufficient evidence with respect to the hair growth effects of adenosine in men and topical application is recommended. In contrast, there is insufficient evidence regarding its efficacy in women, and given its minor adverse reactions and the fact that products for women are commercially available, topical application is permissible.

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CQ7: IS TOPICAL CARPRONIUM CHLORIDE EFFECTIVE?

Grade of recommendation: C1.

Recommendation: Topical carpronium chloride is permissible.

Commentary: With regard to the efficacy of carpronium chloride, four case series and one non-RCT on MPHL have been conducted. Trials involving female subjects have been performed, but no trial examined the clinical effects on FPHL.

In a double-blind non-RCT, involving six male subjects, with an observation period of 1 month, who used 5% carpronium chloride, decreased hair loss or hair growth was observed in four of six subjects, and carpronium chloride was considered effective. Conversely, none of the placebo not containing carpronium was effective.[82]

In a case series involving four male subjects, with an observation period of 77–129 days using topical medication containing 10% carpronium chloride,[83] inhibited hair loss and moderate hair growth were observed in two of four subjects, suggesting that this solution was considered effective.

In a case series involving five male subjects, with an observation period of 3–6 months that used topical medication containing 5% carpronium chloride,[84] the results showed that it was somewhat effective in three of five subjects.[84]

In a case series involving 30 subjects with MPHL, with an observation period of 3 months that used topical medication containing 1% carpronium chloride with added herbal tinctures of *Kashuu* and *Chikusetsuninjin*, it was effective or more than effective in 20% of the subjects and moderately effective or more than moderately effective in 60.0% of the subjects. Female patients were included in this study, but the male-to-female ratio was not mentioned.[85] In addition, in a case series involving 75 male subjects and 11 female subjects, with an observation period of 24 weeks that used a hair growth agent containing 2% carpronium chloride in addition to the aforementioned herbs and *Hinokitiol*, the improvement rate was 26.7% and 54.5% in men and women, respectively.[86]

As described above, the efficacy of topical carpronium chloride has not been sufficiently verified at this stage. However, in view of the fact that 5% carpronium chloride has long been covered by Japanese health insurance, and the vast body of clinical results in Japan of its use in combination with herbs, topical carpronium chloride is permissible.

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CQ8: IS TOPICAL *T*-FLAVANONE EFFECTIVE?

Grade of recommendation: C1.

Recommendation: Topical *t*-flavanone is permissible.

Commentary: Two non-RCT and one RCT were conducted on the efficacy of *t*-flavanone on MPHL, but no clinical trial has been conducted on FPHL.

In a non-RCT involving 14 male subjects with an observation period of 6 months that used a hair growth agent containing *t*-flavanone, hair diameter increased. Particularly, the mean diameter of newly grown hair increased by approximately 20% compared with that before the trial. The number of fallen hairs was also significantly decreased (≦20%) at 4 and 6 months of topical application, whereas no change was found in the placebo group.[87]

In a non-RCT involving 197 male subjects, with an observation period of 30 weeks that used a hair growth agent containing *t*-flavanone and a commercially available hair growth agent (unknown constituents), the rate of moderate or better improvement was also 53.1%, 34.8% and 17.9% in the *t*-flavanone-containing hair agent group, commercially available hair agent group and placebo group, respectively. The *t*-flavanone-containing and commercially available hair agent groups showed a significantly better improvement than the placebo group. The number of terminal hairs whose hair diameter was equal to or thicker than 40 μm increased in the *t*-flavanone-containing and commercially available hair agent groups, whereas it decreased in the placebo group.[88]

Moreover, in an RCT involving 77 male subjects with an observation period of 30 weeks that used hair growth agents containing 0.1% and 0.5% *t*-flavanone, the rate of moderate or better improvement was approximately 40%, 75% and 70% in the placebo group, 0.1% *t*-flavanone-containing hair growth agent group and 0.3% *t*-flavanone-containing hair growth agent group, respectively.[89] Meanwhile, no reliable studies suggested the efficacy of *t*-flavanone on FPHL.

As described above, there is weak evidence that suggests the efficacy of *t*-flavanone on MPHL, and topical application is permissible. In contrast, although there is insufficient evidence that suggests its efficacy on FPHL, in light of its mild adverse reactions, topical application is permissible.

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CQ9: ARE TOPICAL CYTOPURINE AND PENTADECANE EFFECTIVE?

Grade of recommendation: C1.

Recommendation: Topical cytopurine (CTP) and pentadecane are permissible.

Commentary: One RCT on the efficacy of CTP on MPHL has been conducted, but no clinical trials have been conducted on FPHL. With regard to the efficacy of pentadecane, one RCT on MPHL and one case series on FPHL have been conducted. First, with respect to MPHL, an RCT involving 43 male subjects, with an observation period of 16 weeks that used a hair growth agent containing 0.5% CTP has been conducted. With regard to the condition of sparse terminal hair growth and vellus hair, 19% and 5% of the CTP and control groups, respectively, experienced improvement in the condition of sparse terminal hair growth, whereas 14% and 0% of the CTP and control groups, respectively, experienced improvement in the condition of vellus hair. Although the total number of fallen hairs and the number of hairs whose diameter was 40 μm or thicker at 16 weeks decreased in both the CTP and control groups compared with that before the trial, a significant decrease was observed in the CTP group only. With regard to the overall improvement in the findings of the hair and scalp, moderate or better improvement was observed in 30% and 7% of the CTP and control groups, respectively.[90]

In an RCT involving 75 male subjects with an observation period of 24 weeks that used a hair growth agent containing 2.5% pentadecanoic acid glyceride (PDG), the effective rate of those that showed a minor response or better was 76% and 32% in the PDG and control groups, respectively, and it was significantly higher in the PDG group than in the control group.[91]

Subsequently, with respect to FPHL, in a case series involving 33 female subjects, with an observation period of 6 months that used a hair growth agent containing 2.5% PDG and 0.2% tocopherol acetate, overall improvement was evaluated on a scale of five based on the amount of fallen hair during hair washing, growth of vellus hair, transition from vellus hair to terminal hair and findings about the hair. Changes in hair diameter and the increase rate of hair diameter were also evaluated by measuring the hair diameter at hair root and at 6 cm from the root and by calculating their ratio. Evaluation of the overall improvement, based on findings about the hair, showed that the efficacy rate wherein a moderate or better improvement considered effective was 79%. With regard to the improvement rate (moderate improvement or better) for hair findings, it was 76%, 64% and 76% for changes in the amount of fallen hair during hair washing, growth of vellus hair and transition from vellus hair to terminal hair, whereas the increase rate of hair diameter was 4.1%.[92]

As described above, there is weak evidence that suggests the efficacy of CTP and pentadecane for hair growth, and topical application of hair growth agents containing CTP and pentadecane is permissible in view of their mild adverse reactions.

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CQ10: IS TOPICAL KETOCONAZOLE EFFECTIVE?

Grade of recommendation: C1.

Recommendation: Topical ketoconazole (KCZ) is permissible.

Commentary: One non-RCT and two case series on the efficacy of topical KCZ on MPHL were conducted, but no clinical trials have been conducted on FPHL.

First, in a non-RCT involving 27 male subjects, with an observation period of 21 months that used a 2% KCZ shampoo and a commercially available shampoo, pilary index (PI) = anagen hair percentage (A%) × mean hair diameter (Dμm) increased at 6 months in the 2% KCZ group and plateaued at 15 months. Meanwhile, PI levels gradually decreased with time in the control group (12 subjects).[93]

Subsequently, in a case series involving six male subjects, with an observation period of 10–12 months that used a cream containing 2% KCZ, marked hair growth, as evaluated by a dermatologist, was observed in two of six subjects.[94]

Moreover, in a case series involving 17 male subjects, with an observation period of 6 months that used a 2% KCZ lotion, 10 and seven subjects had severe and moderate degrees of hair loss before administration, respectively. Evaluation of improvement by a dermatologist revealed that the distribution improved in one, 12 and four subjects with severe, moderate and minor degrees of hair loss after 6 months of treatment, respectively.[95]

In a non-RCT involving 10 male subjects, with an observation period of 12 months that used a 2% KCZ shampoo and oral administration of finasteride (1 mg daily) in combination, hair growth, and degree of hair loss were also evaluated on a scale of five by three dermatologists. No significant difference was found between the oral administration of finasteride, and combined use of 2% KCZ shampoo and oral administration of finasteride.[96]

As described above, there is weak evidence that suggests the efficacy of the topical application of KCZ for hair growth in MPHL, and topical application is permissible. In contrast, although evidence was insufficient regarding its efficacy for FPHL, in view of their mild adverse reactions, topical application is permissible.

It should be noted that KCZ is not approved in Japan as a hair growth agent.

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CQ11: IS USE OF WIGS EFFECTIVE?

Grade of recommendation: C1.

Recommendation: Use of wigs is permissible.

Commentary: Two case series were conducted on the effectiveness of wearing a wig.[97,98] In a case series involving 26 male subjects where a questionnaire survey was conducted before and after the use of a wig,[97] the QOL of the patients was objectively evaluated using the Psychological Impact of Assistive Device Scale (PIADS) and the VAS. On PIADS, the total score (30.77), competence (1.25), adaptability (1.167) and self-esteem (1.125) significantly increased ($P < 0.001$, Mann–Whitney *U*-test) compared with that before use (0). The total score, competence, adaptability and self-esteem on PIADS all showed a positive correlation ($P < 0.05$, Spearman's rank correlation coefficient) with the change in satisfaction on VAS. Furthermore, the total score, competence, adaptability and self-esteem on PIADS showed a positive correlation ($P < 0.05$, Spearman's rank correlation coefficient) with severity based on the Norwood–Hamilton classification. Adverse reactions caused by using wigs have not been reported.

In a case series involving 20 female subjects where a questionnaire survey was conducted before and after using a wig,[98] the total score (32.55), competence (1.221), adaptability (1.242) and self-esteem (1.306) significantly increased ($P < 0.001$, Mann–Whitney *U*-test) compared with that before use (0) on PIADS, which is used to objectively evaluate the QOL of patients. The change in satisfaction was evaluated using VAS, but no correlation was found with the evaluation items of PIADS. No correlation was also found between PIADS and severity based on the Tajima score. Although the use of wigs led to an improvement in the QOL of female subjects, regardless of severity, improved QOL did not result in increased satisfaction. Adverse reactions caused by wearing wigs have not been reported.

As described above, although the use of a wig does not improve symptoms of hair loss, its use is permissible, when conventional treatments are not successful in improving the symptoms, and the QOL is reduced.

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CQ12: ARE TOPICAL BIMATOPROST AND LATANOPROST EFFECTIVE?

Grade of recommendation: C2.

Recommendation: Topical bimatoprost and latanoprost are not recommended.

Commentary: Bimatoprost, a prostamide F2α derivative whose conventional use was for reducing intraocular pressure in glaucoma, and latanoprost, a similar prostaglandin F2α derivative, have come to be used as eyelash growth enhancers.[99,100] In Japan, bimatoprost is commercially available. One RCT on the efficacy of the topical application of latanoprost for MPHL was conducted.[101]

In an RCT involving 16 male subjects (mean age, 23–35 years, Hamilton classification II–III) with an observation period of 24 weeks where 0.1% latanoprost was used, evaluation of hair growth effects by bilateral comparison against the placebo control group was performed, and 50%, 44% and 6% of those in the treatment group experienced improvement, no change and exacerbation, respectively. Photographic analysis also showed increased hair density in the treatment group.[101]

It should be noted that latanoprost is not approved as an external drug for treating hair follicles in Japan. The safety of these drugs when externally applied to an extensive area is not also established because they are expensive, and the financial burden they pose is not small.

Bimatoprost has shown hair growth effect in an organ culture of hair follicles derived from the human scalp,[102] and bimatoprost may possibly have a hair growth effect on hair other than eyelashes. However, no clinical trials have been conducted.

As described above, the efficacy of topical application of bimatoprost and latanoprost is not sufficiently verified currently, and it is not recommended.

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CQ13: ARE INTRODUCTION OF GROWTH FACTORS AND CELL TRANSPLANTATION THERAPY EFFECTIVE?

Grade of recommendation: C2.

Recommendation: Introduction of growth factors and cell transplantation therapy are not recommended.

Commentary: Direct transplantation of mesenchymal cells with hair-inducing ability or injection of a product derived from the culture supernatant that contains their secreted material to the area of hair loss have been attempted to promote hair growth.[103] Particularly, RCT and case series have been conducted on the hair growth promoting effects of the material derived from the culture supernatant of adipose tissue-derived stem cells and of the platelet-rich plasma.[104–106]

However, most of these clinical trials are limited to certain centers and are in the advanced medical care phase that requires approval of the ethics committee. Their validity, including safety, is not sufficiently verified.

As described above, although introduction of growth factors and cell transplantation therapy are promising treatment methods, many of these must be performed in accordance with regulations, such as the Law on Securing the Safety of Regenerative Medicine, in Japan and they are not widely available to the general public. Therefore, they are not recommended.

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CQ14: IS ORAL ADMINISTRATION OF MINOXIDIL EFFECTIVE?

Grade of recommendation: D.

Recommendation: Oral administration of minoxidil should not be performed.

Commentary: No clinical trials have been conducted on the efficacy of oral administration of minoxidil.

Minoxidil was developed as an antihypertensive agent, but it has not been approved in Japan. It is also not approved as a treatment drug for MPHL in any country. Nevertheless, physicians prescribe it without giving it much thought, and lay people acquire it through private importation based on its adverse reactions, including generalized hirsutism. This has been regarded as a problem from the viewpoint of the Law on Pharmaceuticals and Medical Instruments in Japan.

There are few reports on the adverse reactions of the oral administration of minoxidil other than hypertrichosis, but the post-marketing survey column on the attached document of an orally administrated pharmaceutical lists serious cardiovascular disorders, such as chest pain, tachycardia, palpitations, breathlessness, dyspnea, congestive heart failure, edema and weight gain.

As described above, the benefits and risks of oral therapy with minoxidil have not been sufficiently verified, and it is strongly contraindicated for MPHL and FPHL.