学位論文

「Long-term (10-year) efficacy of finasteride

in 532 Japanese men with androgenetic alopecia」

（男性型脱毛症の日本人男性 532 症例における

フィナステリド治療についての長期間（10 年間）有効性調査）

DM-16031　　栁澤　正之

北里大学大学院医療系研究科　医学専攻博士課程
臨床医科学群　形成外科・美容外科
指導教授　武田　啓

著者の宣言

　本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

要旨

男性型脱毛症（Androgenetic Alopecia: AGA）は思春期以降の男性において頭髪が進行性に薄くなる脱毛症である。AGA はテストステロンがⅡ型 5α 還元酵素により変換されるデヒドロテストステロン（DHT）の影響で進行する。フィナステリドはⅡ型 5α 還元酵素を阻害し、DHT 産生を抑制することで AGA の治療に用いられる。フィナステリドは AGA の治療薬として 2005 年に日本で認可、処方開始された。現在では広く世界 60 か国以上で認可、処方され、300 万人以上が内服している。AGA に対するフィナステリド(1mg/日)の効果と安全性については複数の大規模研究、長期間研究が報告されているが、知り得る限り日本において 5 年以上の治療報告はなく、また世界的にも 10 年を超える治療報告は稀である。本研究の目的は、日本においては初となり、また世界的にも少ない大規模かつ長期間(10 年)のフィナステリド治療の有効性と安全性を評価することである。我々はフィナステリド 1 ㎎/日の内服による AGA 治療を 10 年間継続した 532 人の日本人男性について　治療有効性調査を行った。有効性は Norwood-Hamilton 分類（N-H 分類）と頭髪写真について 7 段階評価を行う modified global photographic assessment score (MGPA)を用いて評価した。

フィナステリド 1 ㎎/日の内服による 10 年間 AGA 治療の結果、改善例(MGPA≧5)は 91.5%(487/532)、進行予防例(MGPA≧4)は 99.1%(527/532)に認められた。また、全体の N-H 分類は治療前と 10 年間治療後を比べると約 1 グレード改善した。全体を初診時 N-H: Ⅰ/Ⅱ/Ⅲ群と初診時 N-H:Ⅳ/Ⅴ/Ⅵ/Ⅶ群とに分けてを比較すると、10 年後 MGPA について有意な差を認めた。(6.27±0.62 vs 5.52±0.78) (p<0.001)また本研究では、AGA 治療成績評価として、医師による頭髪写真の客観的評価だけでなく、被験者のアンケートによる自身の主観的評価についても評価を行った。AGA 治療の被験者の主観的評価を調査した研究は世界的にも数が少なく、また長期間の AGA 治療に追従した主観的評価は他に例を見ない。主観的評価としての数値化したアンケートの回答についてそれぞれの項目で有意な差を認めた。(p<0.001)

AGA の日本人男性におけるフィナステリド 1mg 錠の長期治療は、主観的評価、客観的調査の両方で高い有効性を認めた。

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「Long-term (10-year) efficacy of finasteride in 532 Japanese men with androgenetic alopecia」

ABSTRACT

Finasteride is a standard medical treatment for androgenetic alopecia; however, no long-term study of up to 10 years has been performed in Japan. Therefore, we evaluated the efficacy and safety of 1 mg/day finasteride in 532 Japanese men who were treated for androgenetic alopecia for 10 years. We performed subjective evaluations, using questionnaires administered to patients, in addition to the objective evaluation by doctors. The efficacy was assessed using the Norwood-Hamilton scale and modified global photographic assessment score, the standardized 7-point rating score using scalp photographs. For the Norwood-Hamilton classifications, stages IIa and IIv were combined as II, IIIa and IIIv were combined as III, IVa was combined as IV, and Va was combined as V. The proportions of patients with improvement (score$\geq$5) and prevention of disease progression (score$\geq$4) were 91.5% and 99.1%, respectively. The Norwood-Hamilton classification grading improved by approximately 1 grade from 3.35$\pm$1.11 to 2.55$\pm$1.30 after the 10-year treatment. The groups that showed Norwood-Hamilton: I/II/III and IV/V/VI/VII at the first visit showed statistically significant differences in the modified global photographic assessment score at the 10-year treatment subjective evaluation (6.27$\pm$0.62 vs 5.52$\pm$0.78, P<0.001). Furthermore, the quantitative analysis of the objective evaluation using the questionnaire was also significantly different (P<0.001). During the study period, no serious adverse reaction was recognized. Long-term (10-year) treatment with 1 mg/day finasteride in Japanese men with androgenetic alopecia showed high efficacy in subjective and objective evaluations.

Keywords: androgenetic alopecia, finasteride, Japanese, long-term, modified global photographic assessment, Norwood-Hamilton scale,

INTRODUCTION

Finasteride was authorized in Japan for the treatment of androgenetic alopecia (AGA) in 2005; subsequently, prescription of this medication commenced. Presently, finasteride is authorized in over 60 countries and is administered to over 3 million patients for AGA. Dihydro-testosterone (DHT) has a key role in mediating progressive scalp hair loss in men with AGA, and finasteride blocks the conversion of testosterone to DHT as a selective type II 5α-reductase inhibitor, which justifies its use in AGA treatment. 1)2)3) Although the efficacy of AGA treatment with finasteride has been demonstrated by several large-scale and

long-term studies, 4)5)6)7) no long-term investigation for up to 10 years has yet been conducted in Japanese subjects. 8)9)10) Therefore, the objective of this study was to evaluate the efficacy and safety of large-scale and long-term AGA treatment with finasteride, which, to our knowledge, is the first of such studies in Japan. In this study, a subjective evaluation was conducted using a questionnaire on AGA administered to each patient; moreover, an objective evaluation was performed by doctors.

METHODS

Study population

We examined 532 Japanese men who had been diagnosed with AGA at the first visit to the Tokyo Memorial Clinic Hirayama (hereafter, "the clinic") during the period between December 2005 and January 2009 and had been treated with 1 mg/day finasteride for 10 years until January 2019. Furthermore, all patients answered a questionnaire about the long-term treatment of AGA after 10 years treatment. Written informed consent for participation in the present study was obtained from all patients.

Efficacy Evaluation

Objective efficacy - Scalp photographs

The efficacy was objectively assessed using the Norwood-Hamilton scale (N-H) 11)12) and the modified global photographic assessment score (MGPA) 13)14) (Figure S1), with the following standardized 7-point rating score using scalp photographs: 1, significant disease progression; 2, moderate disease progression; 3, slight disease progression; 4, no change; 5, slight improvement; 6, moderate improvement; and 7, significant improvement. In the N-H classifications, stages IIa and IIv were combined as stage II, IIIa and IIIv were combined as III, IVa was combined as IV, and Va was combined as V. In the MGPA assessment, we evaluated scalp photographs at the first visit and yearly and categorized the MGPA in every N-H classification at the first visit (Figure S2).

Subjective efficacy - Questionnaire

The subjective efficacy was assessed using a long-term AGA treatment questionnaire, which was digitalized to the following numerical rating scale (NRS: 0-3: slightly, 4-6: moderate, 7-10: significant). 15)16) (Figure S3) Questionnaire items were as follows. Q1: To what degree are you satisfied with your treatment? Q2: To what degree do you feel your hair has improved? Q3: To what degree do you wish to continue treatment? Q4: How would you compare your hair loss to the hair of people of the same age pre-treatment? Q5: How would you compare your hair loss to the hair of people of the same age 10 years post-treatment? Numerical variables of the results are presented as summary statistics (mean ± standard

deviation); the data were analyzed using Welch's t-test for the efficacy evaluation. Statistical analyses were performed using Microsoft Excel Statistics program version 2.14; a P<0.05 was considered statistically significant.

Safety Evaluation

Adverse reactions were recorded to evaluate safety by questionnaire.

RESULTS

Patient Characteristics

The characteristics of all patients evaluated for AGA treatment efficacy were as follows: age at first visit, 37.8 ± 10.0 years; age range, 20–69 years; and values of each N-H at the first visit: I/II/III/IV/V/VI/VII, 6/116/204/124/61/18/3, respectively.

Efficacy Evaluation in 10 years treatment

Objective efficacy - Scalp photographs

The proportions of patients with improvement (MGPA≥5) or prevention of disease progression (MGPA≥4) at treatment year 10 were 91.5% (487/532) and 99.1% (527/532), respectively. The efficacy evaluation showed that the MGPA improved significantly from year 1 through to year 10 of treatment compared with the baseline (MGPA = 4). The MGPA of each N-H group was linear according to the N-H number; the total was between N-H:III and N-H:IV. (Figure S4) (Table S1) Receiver operating characteristic curve (ROC) analysis was performed to classify patients with improvement (MGPA≥5) and deteriorating (MGPA<5) condition at year 10 of treatment; the cut-off point was N-H: III. (the area under the curve [AUC], which indicates the predictive value, was 0.746.). Furthermore, the MGPA of the total study population and the N-H:I/II/III group at the first visit improved from year 5 through to year 10, with statistically significant differences (P<0.001). The early stage AGA group (N-H: I/II/III at first visit) showed more improvement with long-term AGA treatment (10-year) with finasteride than the other groups did in the objective evaluation. The N-H classification of AGA patients improved by approximately 1 grade over the 10-year treatment with finasteride; significant differences were observed from pre-treatment (3.35±1.11) to post-treatment (2.55±1.30, P<0.001) in comparison of digitized classification.

Subjective evaluation - Questionnaire

The high subjective efficacy of AGA treatment was revealed by the answers to Q1, "To what degree are you satisfied with your treatment?" (7.09±1.78); Q2, "To what degree do you feel your hair has improved?" (6.95±1.82), and Q3, "To what degree do you wish to continue treatment?" (8.26±1.84).

A significant difference was observed between Q4 and Q5 (pre- and 10-year post-treatment, 3.41±2.12 and 4.93±2.21, respectively, P<0.001) (Table S2) Furthermore, a comparison between the N-H: I/II/III and N-H:IV/V/VI/VII groups at first visit revealed a statistically significant difference in the answer to Q 1, 2, 4, and 5 (P<0.001) and Q3 (P<0.05). The early stage AGA group (N-H: I/II/III at first visit) also showed a greater improvement following long-term (10-year) treatment with finasteride than the other groups did in the subjective evaluation.

Safety Evaluation

During the study period for 10 years, no serious adverse reaction was recognized.

Mild and temporary adverse reactions were recorded in 6.8% (36/532) of the entire study population by questionnaire. The adverse reactions were decreased libido (5.6%, n=30) and erectile dysfunction (3.0%, n=16). All adverse reactions were mild and all patients continued treatment for 10 years.

DISCUSSION

Efficacy Evaluation

Objective evaluation - Scalp photographs

We evaluated the long-term (10-year) efficacy and safety of AGA treatment with 1 mg/day finasteride in a large study population (532 patients), as the first study of this kind in Japan, to our knowledge. A high objective efficacy was demonstrated by the MGPA, which revealed improvement and prevention of disease progression in 99.1% of the 532 Japanese men with AGA treated with 1 mg/day finasteride for 10 years. Furthermore, the outcome was similar to or better than that reported by other studies in Japan. 8)9)10)13)17) Differences have been known to occur in the progression of AGA symptoms between Japanese and Caucasian men. 8) 18) This efficacy of the investigated treatment in Japanese men exceeded that reported in other studies in Caucasians. The superior response of Japanese men with AGA was reported to likely be attributable to their hair characteristics (greater diameter, black color, and lower density), which facilitated the detection of slight changes. 10) 19)-23) A novel finding observed in this study was the significant difference in the improvement of AGA following finasteride treatment between the N-H: I/II/III and N-H: IV/V/VI/VII groups at the first visit. The ROC analysis revealed a similar difference, that was performed to classify patients with improvement (MGPA≥5) and deteriorating (MGPA<5) condition at year 10 of treatment; the cut-off point was N-H: III (AUC: 0.746). Furthermore, the MGPA of the total study population and the N-H: I/II/III group at the first visit significantly improved from treatment year 5 to 10 (P<0.001). This efficacy was different from that of a 5-year study in Japanese men, which reported that the efficacy began to plateau after 4 years of treatment. 10) Several

studies have reported that AGA progresses in N-H classification with age, 7)11)12)18) and that younger patients show more improvement than that of older patients with AGA treatment. 24)25) In this study, AGA patients at the early stage of N-H classification showed more improvement than patients at the later stage did.

Subjective evaluation - Questionnaire

Several studies using questionnaires on AGA administered to patients and doctors have been reported. 26)27)28) We evaluated the questionnaires administered to patients with AGA who were treated with finasteride for 10 years. A highly subjective efficacy was revealed by all answers to the questionnaires. Especially, the analysis showed that the score of the response to Q3; "To what degree do you wish to continue treatment?" was high (8.26 ± 1.84), which could be attributed to the fact that the patients had undergone the treatment for 10 years already. However, the subjective efficacy of long-term treatment of AGA with finasteride was evident based on the differences in the results between Q4 and Q5 (pre- and post-treatment, 3.41 ± 2.12 and 4.93 ± 2.21, respectively, $P < 0.001$). A high efficacy and significant difference in improvement of AGA with finasteride treatment was also observed between the N-H: I/II/III and N-H: IV/V/VI/VII groups at first visit in the objective evaluation using the questionnaire.

Safety evaluation

Adverse reactions were recorded in 6.8% (36/532) in the safety evaluation in this study, which was slightly higher than that observed in other studies in Japanese men. 8)9)17) This observation was thought to have been caused by the fact that the investigation period of this study was longer than that of others and, therefore, the patients had aged more. Incidences of decreased libido and erectile dysfunction have been known to increase in proportion with age. In the investigation in 40 years or older of Asians, the incidences of decreased libido and erectile dysfunction were 6.0–38.7% and 40.6–70.0%, respectively. 29)30) Overall, the adverse reactions were all mild, and the incidence was lower than the generic incidence of decreased libido and erectile dysfunction in Asians. As adverse reactions were recorded by patients in a subjective questionnaire, the result was thought to be slightly different from the correct number of adverse reactions in this study. Strict safety evaluation was not investigated in this study. Several studies on AGA treatment with finasteride have reported that there are no significant differences from the placebo in adverse reactions, 13)31) and that the risk of discontinuing the treatment because of adverse reaction is similar to that of the placebo. 32) In summary, long–term (10-year) AGA treatment with finasteride 1 mg/day demonstrated a high efficacy and safety based on subjective and objective evaluations in Japanese men. Specifically, the N-H classification of AGA patients improved by approximately 1 grade after 10 years of treatment with finasteride. Furthermore, a novel discovery of this study was that

the group with N-H:I/II/III at the first visit showed greater improvement than the group with N-H: IV/V/ VI/VII at first visit, following 10 years of AGA treatment with finasteride. We recommend that AGA patients should start treatment with 1 mg/day finasteride at the early stage of classification of AGA (within N-H: I, II, or III) for adequate efficacy.

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Conflict of interest statement
The authors state no conflict of interests.

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Figure 1.

The modified global photographic assessment score (MGPA), with the following standardized 7-point rating score using scalp photographs: 1, significant disease progression; 2, moderate disease progression; 3, slight disease progression; 4, no change; 5, slight improvement; 6, moderate improvement; and 7, significant improvement.

Scalp photographs of representative patient's for evaluation of MGPA.

Vertex photographs and (or) forehead photographs were taken for every patient at each examination and used for evaluation.

(There is no display about cases of MGPA: 1/2/3)

A: Base line (MGPA=4) (Vertex photograph at first visit)

B: Base line (MGPA=4) (Forehead photograph at first visit)

C: MGPA=5 (Vertex photograph at 6 months of treatment)

D: MGPA=5 (Forehead photograph at 6 months of treatment)

E: MGPA=6 (Vertex photograph at 24 months of treatment)

F: MGPA=6 (Forehead photograph at 24 months of treatment)

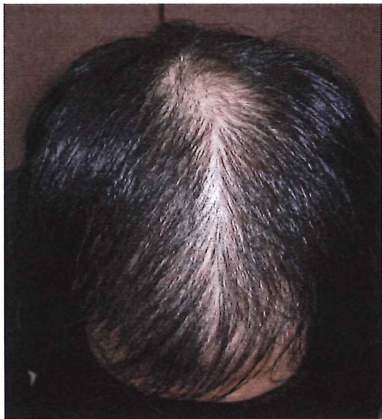G: MGPA=7 (Vertex photograph at 60 months of treatment)

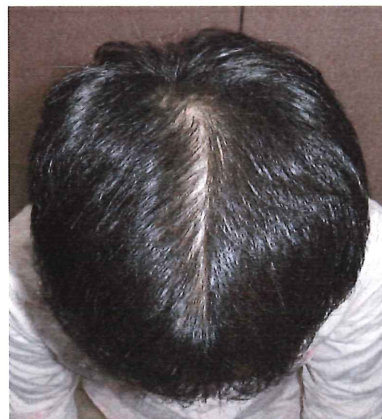H: MGPA=7 (Forehead photograph at 60 months of treatment)
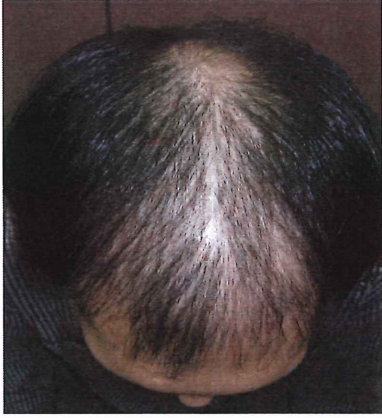
A.

B.

C.

D.

E.

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G.

H.

Figure 2.

Scalp photographs at the first visit and yearly, were evaluated about MGPA and N-H.

A: at first visit
B: at 1 year of treatment
C: at 2 years of treatment
D: at 3 years of treatment
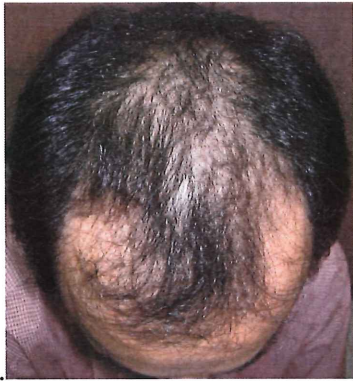E: at 4 years of treatment
F: at 5 years of treatment
G: at 6 years of treatment
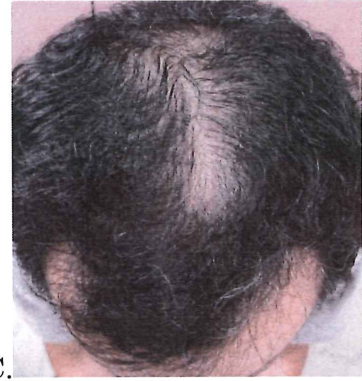H: at 7 years of treatment
I: at 8 years of treatment
J: at 9 years of treatment
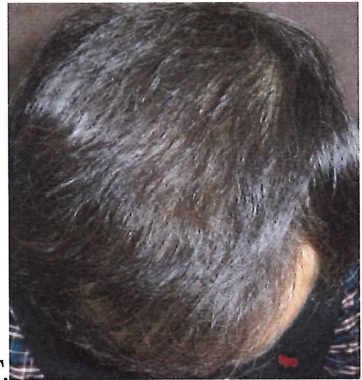K: at 10 years of treatment
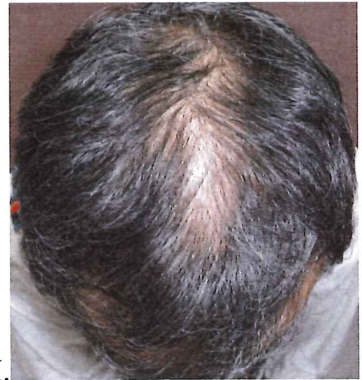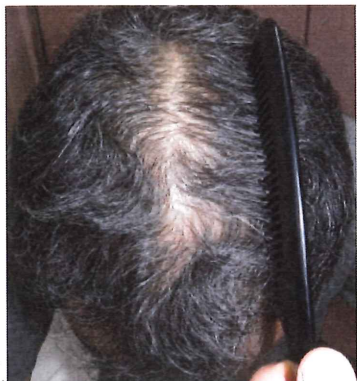
A.

B.

C.

D.

E.

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G.

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I.

J.

K.

Figure 3.

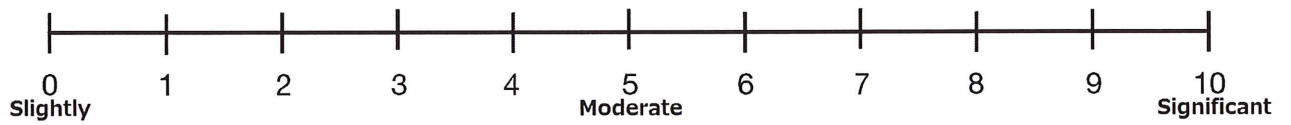Numerical Rating Scale (NRS): the standardized 11-point rating was scored by patients themselves: entry example.

Figure 4.

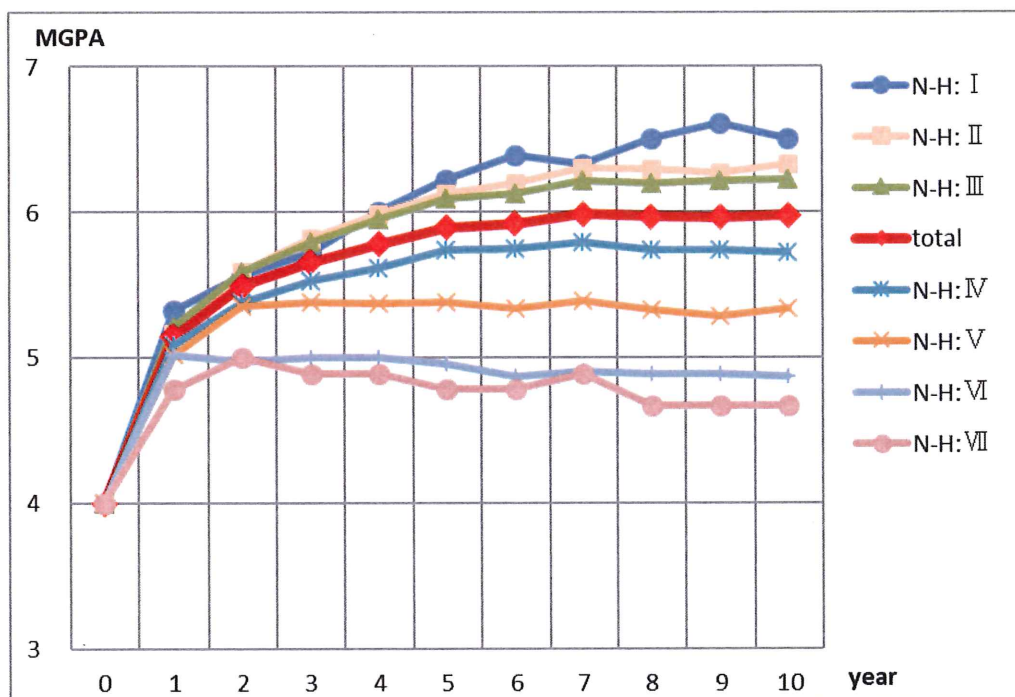Changes in MGPA on each N-H group at first visit.

Table 1.

Changes in modified global photographic assessment scores (MGPA) from before treatment through to year 10 in each Norwood-Hamilton scale (N-H) group at first visit

N-H	number	0Y	1Y	2Y	3Y	4Y	5Y	6Y	7Y	8Y	9Y	10Y
I	6	4.00	5.33±0.51	5.56±0.50	5.72±0.62	6.00±0.64	6.22±0.53	6.39±0.65	6.33±0.64	6.50±0.63	6.61±0.49	6.50±0.57
II (a,v)	116	4.00	5.17±0.61	5.59±0.70	5.82±0.72	5.99±0.75	6.13±0.67	6.20±0.68	6.30±0.65	6.29±0.67	6.27±0.70	6.33±0.66
III (a,v)	204	4.00	5.21±0.47	5.59±0.53	5.79±0.55	5.95±0.56	6.09±0.58	6.13±0.61	6.21±0.59	6.20±0.61	6.21±0.60	6.22±0.59
IV(a)	124	4.00	5.09±0.42	5.38±0.50	5.53±0.57	5.62±0.60	5.74±0.62	5.75±0.67	5.79±0.73	5.74±0.73	5.74±0.74	5.72±0.79
V (a)	61	4.00	5.02±0.29	5.35±0.41	5.38±0.40	5.37±0.46	5.38±0.53	5.34±0.52	5.39±0.58	5.33±0.64	5.28±0.68	5.34±0.61
VI	18	4.00	5.02±0.36	4.98±0.38	5.00±0.29	5.00±0.27	4.96±0.47	4.87±0.55	4.91±0.49	4.89±0.58	4.89±0.66	4.87±0.64
VII	3	4.00	4.78±0.31	5.00±0.27	4.89±0.42	4.89±0.42	4.78±0.31	4.78±0.31	4.89±0.42	4.67±0.27	4.67±0.27	4.67±0.27
total	532	4.00	5.14±0.51	5.49±0.59	5.66±0.62	5.78±0.66	5.89±0.68	5.92±0.72	5.99±0.73	5.96±0.77	5.96±0.78	5.98±0.78

Mean ±Standard Deviation (Mean ±SD) *, there were significant differences in MGPA at year 10 between N-H:I/II/III and N-H:IV/V/VI/VII groups ($P<0.001$).

Table 2.

Numerical analysis of answers to questionnaire using numerical rating scale (NRS)

Q1	7.09	±	1.78
Q2	6.95	±	1.82
Q3	8.26	±	1.84
Q4	3.41	±	2.12
Q5	4.93	±	2.21

Mean ±SD *

Q1: To what degree are you satisfied with your treatment?

Q2: To what degree do you feel your hair has improved?

Q3: To what degree do you wish to continue treatment?

Q4: How would you compare your hair loss to the hair of people of the same age pre-treatment?

Q5: How would you compare your hair loss to the hair of people of the same age 10 years post-treatment?