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Is Minoxidil Efficacious and Safe for the Treatment of Androgenetic Alopecia (AGA) in Men, and If So, What Is the Optimal Strength and Means of Delivery?

Anhthu P. Pickart
Philadelphia College of Osteopathic Medicine, anhthupi@pcom.edu

Is minoxidil efficacious and safe for the treatment of androgenetic alopecia (AGA) in men, and if so, what is the optimal strength and means of delivery?

Anhthu P. Pickart, PA-S

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not minoxidil is efficacious and safe for the treatment of androgenetic alopecia (AGA) in men, and if so, what is the optimal strength and means of delivery.

Study Design: Review of three double-blind randomized controlled trials studying men (18-49 y/o) with androgenetic alopecia published in English from 2007-2009.

Data Source: Three articles of double-blind randomized controlled trials found via PubMed.

Outcomes Measured: Outcomes measured included the efficacy and safety of minoxidil as well as the optimal strength and means of delivery of the drug. For efficacy, parameters used included target area hair count (TAHC), subject assessment using rating scale, expert panel or investigator assessment via photographic review and then rated on the same scale used by subjects. To assess safety, the studies used subject report of symptoms of scalp irritation, investigator examination of signs of scalp irritation, and change in vital signs and/or abnormal lab values for systemic effects. As for the optimal strength and means of delivery, this was evaluated based on the way each study was designed. In the Olsen study, 5% minoxidil foam applied twice daily was compared to a placebo, while the Tsuboi study compared application of 5% minoxidil lotion to 1% minoxidil lotion with both also applied twice daily, and the Shin study compared the use of a placebo in the morning and 5% minoxidil/0.01% tretinoin in the evening against twice daily application of 5% minoxidil alone.

Results: The Olsen and Tsuboi studies demonstrated that 5% minoxidil applied twice daily was efficacious without significant adverse effects when compared to placebo or 1% minoxidil respectively, and the Shin study raised the possibility of combined 5% minoxidil/0.01% tretinoin to obtain similar efficacy without significant adverse effects with only once daily usage.

Conclusion: Minoxidil is safe and efficacious in the treatment of male AGA especially at the strength of 5% in either foam or solution preparation for twice daily use.

Key Words: minoxidil, androgenetic alopecia, men

Introduction

Male androgenetic alopecia (AGA), also known as male pattern hair loss (MPHL), is characterized by the miniaturization of the hair follicles in the frontal and parietal scalp.[1] It is the most common form of alopecia in men with most men developing some degree of recession of the hairline during their lifetime, and although prevalence may vary, severe MPHL can be seen in around 50% of men beyond age 40.[2,3] In 2012, there were 704,593 male patients worldwide that sought care for MPHL.[4] Of these, 458,271 were nonsurgical patients, and 246,321 were treated with hair restoration surgery.[4] Considering these numbers, physician assistants can expect to encounter men with this condition frequently in our practice whether it may be in a primary care or a more specialized dermatologic setting.

There is no exact number for the total health care cost of treating male AGA, and the cost varies significantly depending on the type of treatments. For example, the median cost of minoxidil for one month use varies from $16.04 for Rogaine Mens External 5% foam, to $27.37 for Rogaine Mens Extra Strength External 5% foam.[5] For those opting for hair restoration surgery, it can be done via one of two ways: follicular unit transplantation (FUT) or follicular unit extraction (FUE).[6] The cost for FUT ranges from $3-$9 per graft depending on the location of the practice, while FUE can cost anywhere from $6.50-$12 per graft.[6]

As for the cause of male AGA, there is not one defining etiology, rather this condition develops as a result of various factors with the two most contributory being androgen hyperactivity and genetic predisposition to hair loss related sensitivity to androgen actions.[2] Dihydroxytestosterone (DHT) synthesized from testosterone by an enzyme called 5α-reductase is thought to be the principal agent responsible for MPHL.[2] DHT binds more potently to androgen receptors than testosterone and is found localized to hair follicles.[2] Consistent higher levels of

5α-reductase as well as DHT are found in men with MPHL versus those without balding scalps.[2] Additionally, some men have genetically more enhanced androgen receptors that are more responsive to the actions of DHT, and thus are more likely to develop AGA.[2] Male AGA often presents clinically with consistently identifiable patterns as categorized by the Hamilton-Norwood classification ranging from type I-VIII based on the severity of hairline recession.[2]

Male AGA is a progressive condition, and there is currently not one treatment that is considered to be the gold standard. Currently, two FDA-approved pharmaceutical options used for male AGA are topical minoxidil and oral finasteride.[2] Finasteride is a 5α-reductase inhibitor that works to prevent the conversion of testosterone to DHT, and as DHT is the principal agent responsible for MPHL, decreased DHT means a decrease in hair loss.[7] Minoxidil, on the other hand, has no known mechanism of action like finasteride. It was first developed to be an oral antihypertensive agent, and hypertrichosis was observed as a side effect in some patients, which led to its formulation as a topical agent for AGA.[8] Minoxidil was observed to enhance the size of the hair follicles and stimulate and prolong the anagen (growth) phase of the hair cycle, resulting in increased hair count and thicker hair shafts that stay on the scalp for a longer period of time.[2,8]

In addition to pharmaceutical therapy, other treatment methods include low-level laser light therapy or hair restoration surgery.[2] The mechanism of action of laser light therapy is not fully understood, and its efficacy is still questionable.[2] As for hair restoration surgery, it is the only permanent but also the most invasive method to treat male AGA. Besides these treatment options, nonmedical therapy is also available in the form of hairpieces.[2]

Minoxidil, when compared to the medical alternatives, is the least invasive form of treatment due to its delivery as a topical agent with minimal systemic absorption.[2] Nevertheless, minoxidil has been suggested to cause tachycardia, hypotension, and even increased incidence of

coronary artery disease in a subset of men with AGA due to its origin as an antihypertensive agent.[2] Furthermore, it comes in different formulations like foam or combined with tretinoin, and there has been no systematic review to reexamine its safety and efficacy since 2007 as well as to assess the optimal strength and means of delivery.

Objective

The objective of this systematic review is to determine whether or not minoxidil is efficacious and safe for the treatment of AGA in men, and if so, what is the optimal strength and means of delivery.

Methods

In selecting the studies for this review, the author applied the following criteria. The articles had to be double-blind, randomized controlled trials that studied men between the ages of 18 and 49 years with AGA, and all were published in English in peer reviewed journals. The interventions in these studies were various strengths and formulations of minoxidil. The studies compared those in the treatment group receiving minoxidil to those receiving a placebo or a different preparation of minoxidil. The outcomes measured include the efficacy and safety of the various minoxidil interventions in treating men with AGA.

In searching the articles for this review, key words used included minoxidil, androgenetic alopecia, and men. The studies were selected from PubMed for their relevance to the clinical question. Inclusion criteria required that the studies must be randomized controlled trials published after 1/1/2007 with patient oriented outcomes such as improvement in hair growth. Exclusion criteria included females, patients with other medical problems such as uncontrolled hypertension or other scalp conditions, patients that used minoxidil or other hair growth products prior to study, patients with untreated cancer, or history of radiation to the scalp or chemotherapy

within the previous year, or history of hair transplants or scalp reduction surgery, and patients on systemic steroids for more than fourteen days within the last two months. Statistics reported or used included p-values, relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), relative risk increase (RRI), absolute risk increase (ARI), and numbers needed to harm (NNH). Table 1 displays the demographics and characteristics of each study.

Table 1-Demographics and characteristics of included studies

Study	Type	# Pt	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Olsen[9] (2007)	Double blind RCT	352	18-49, mean 39.2	Hamilton-Norwood patterns IIIv, IV, or V male pattern hair loss who were otherwise in good health	(1) known sensitivity to minoxidil, (2) use of any OTC/Rx medication for hair growth within last 6 months, (3) use of 5 alpha-reductase inhibitors, isotretinoin, had radiation to the scalp, or chemotherapy in the previous year, (4) use of botanicals / neutraceuticals for hair regrowth within the prior 3 months, (5) use of systemic steroids > 14 days in the past 2 months. (6) Other exclusions[6]	37	5% minoxidil 1g BID
Shin[3] (2007)	Double blind RCT	31	28-45, mean 39.7 ± 4.5 years	Hamilton-Norwood classification type III-V	other medical problems, use of any products or drugs affecting hair growth for ≥ 6 months prior to the study	2	1. Control group application of 5% minoxidil 1 mL BID 2. Test group-one application of a placebo in the morning and then one application of 5% minoxidil / 0.01% tretinoin at night
Tsuboi[1] (2009)	Double blind RCT	300	≥ 20, mean 40.6 ± 6.65 years	Diagnosed within the last 10 years with AGA as classified by Ogata	None was mentioned in study.	15	Group 1- application of 5% minoxidil 1 mL BID Group 2- application of 1% minoxidil 1 mL BID

Outcomes Measured

Outcomes measured for efficacy included mean change from baseline in hair count, subject assessment, and expert assessment. In the Olsen study, mean change from baseline in hair count was determined via target area hair count (TAHC) at baseline and at conclusion. Subject assessments and expert assessments were recorded on separate 7-point scales with slightly different wordings on each scale as appropriate to each audience. Similarly in the Shin study, efficacy was assessed via macrophotographic image at baseline and at conclusion looking at total hair count, non-vellus hair count, anagen hair ratio, linear hair growth rate, and mean hair diameter. Efficacy was also measured by patient assessment of improvement and satisfaction based on a 10-point scale as well as by expert GPR recorded as one of five gradings. The Tsuboi study also examined efficacy via hair counting at baseline and at conclusion of non-vellus, vellus, terminal, and non-terminal hair as well as assessments of hair growth by subjects and experts using the same 5-point scale.

To assess safety, the studies used subject report of symptoms of scalp irritation (burning, itching, stinging) and investigator examination of signs of scalp irritation (dryness/scaling, folliculitis, erythema). Any finding either mild or moderate reported by subjects or seen by investigators were recorded as having scalp irritation. Safety was also measured via change in vital signs and/or abnormal laboratory values to account for systemic effects.

Results

In order to review the studies the 16th week was chosen as the point of comparison for the Olsen and Tsuboi studies while the closest measured time period of the 18th week was chosen for the Shin study. Additionally, worst-case analyses were done for all studies to ensure the most accurate review. According to Table 2, the mean change from baseline for change in hair

count/cm^2 shows 20.9 for 5% minoxidil foam BID versus 4.7 for placebo, 22.3 for 5% minoxidil solution BID versus 17.2 for 1% minoxidil solution BID, and 17.3 for 5% minoxidil/0.1% tretinoin once a day versus 12.9 for 5% minoxidil solution BID. The Olsen study reported significance with p-value < 0.0001 for the 5% minoxidil versus placebo, and the Tsuboi study reported that the difference between the 5% and 1% groups was significant based on two-sided CI of 1.3-8.8 and a significant p-value of 0.009.[1,9]

Table 2-Efficacy based on change in hair count

Study	Comparison	Mean change from baseline (hair count/cm^2)	P-value
Olsen[9] (2007)	5% minoxidil foam BID	20.9	<0.0001
	Placebo	4.7	
Tsuboi[1] (2009)	5% minoxidil solution BID	22.3	0.009
	1% minoxidil solution BID	17.2	
Shin[3] (2007)	Placebo AM, 5% minoxidil solution / 0.01% tretinoin PM	17.3	NS
	5% minoxidil solution BID	12.9	

In terms of subject assessment and expert assessment of hair growth, results were converted into dichotomous data for both Olsen and Tsuboi studies. Based on the subject assessment, the Olsen study reported 70.6% of the minoxidil patients with improved hair growth as compared to 48.3% of patients on placebo, yielding a significant p-value <0.0001 (Table 3). The corresponding NNT was 5, meaning that for every five patients treated with 5% minoxidil foam BID, one will see slight improvement or better in hair growth as compared to placebo (Table 3). For those with moderate improvement or better in hair growth, the numbers are 48% for 5% minoxidil versus 21.5% for placebo, giving a NNT of 4 (Table 3). The Tsuboi study reported 67% of minoxidil patients on 5% solution saw improvement versus 62% of patients on 1% solution, yielding a non-significant p-value of 0.330 with a NNT of 19 (Table 3). Limited to those with moderate improvement or better, the numbers become 24% versus 16%, resulting in a non-significant p-value of 0.087 with a NNT of 13 (Table 3).

Table 3-Efficacy based on subject and expert assessment

	Study	Comparison	Improvement from baseline	RBI	ABI	NNT	P-value
Subject Assessment of Hair	Olsen[9] (slight or better)	5% minoxidil foam BID	70.6%	46%	22%	5	<0.0001
		Placebo	48.3%				
	Olsen[9] (moderate or better)	5% minoxidil foam BID	48%	122%	26%	4	N/A
		Placebo	21.5%				
	Tsuboi[1] (slight or better)	5% minoxidil solution BID	67%	9%	5%	19	0.33
		1% minoxidil solution BID	62%				
	Tsuboi[1] (moderate or better)	5% minoxidil solution BID	24%	51%	8%	13	0.087
		1% minoxidil solution BID	16%				
	Shin[3]	Placebo AM, 5% minoxidil solution / 0.01% tretinoin PM	4.2	N/A			NS
		5% minoxidil solution BID	3.8				
Expert Assessment of Hair	Olsen[9] (slight or better)	5% minoxidil foam BID	38.3%	94%	19%	6	<0.0001
		Placebo	19.8%				
	Olsen[9] (moderate or better)	5% minoxidil foam BID	8%	1238%	7%	14	N/A
		Placebo	1%				
	Tsuboi[1] (slight or better)	5% minoxidil solution BID	81%	5%	4%	27	0.435
		1% minoxidil solution BID	77%				
	Tsuboi[1] (moderate or better)	5% minoxidil solution BID	31%	80%	14%	8	0.007
		1% minoxidil solution BID	17%				
	Shin[3]	Placebo AM, 5% minoxidil solution / 0.01% tretinoin PM	1.6	N/A			NS
		5% minoxidil solution BID	1.8				

As for the expert assessment, the Olsen study showed 38.3% of patients on minoxidil seeing an improvement in hair growth as compared to 19.8% of those on placebo, yielding a significant p-value <0.0001 with a corresponding NNT of 6 (Table 3). For the moderate improvement, the numbers are 8% versus 1% with a resulting NNT of 14 (Table 3). In the Tsuboi study, no significance was found when assessing slight or better improvement in hair growth, however the results measuring moderate improvement of hair growth show 31% for the 5% group and 17% for the 1% group, yielding a significant p-value of 0.007 with a corresponding NNT of 8 (Table 3). In the Shin study, the mean changes from baseline of 3.8 for 5% minoxidil BID and 4.2 for the combined product based on subject assessment and 1.8 and 1.6 respectively for expert assessment show no significant difference (Table 3).

For measuring safety, the results were converted into dichotomous data with the exception of the Tsuboi study, which did not report any symptoms of scalp irritations, and the Shin study, which did not report any data to account for systemic effects. In the Olsen study, one can see that 6% of patients using 5% minoxidil foam BID experienced at least one of the symptoms of scalp irritation versus 2% of those on placebo (Table 4). The corresponding NNH was 31, meaning that for every 31 patients using 5% minoxidil foam BID, one will experience at least one of the symptoms of scalp irritation as compared to placebo (Table 4). As for the Shin study, this indicated that 31% of patients on the combined product experienced symptoms of scalp irritation versus 27% of those using 5% solution BID alone with a NNH of 22 (Table 4).

Table 4-Safety based on subject report, investigator assessment, and systemic effects

	Study	Comparison	Percentage of Patients with	RRI	ARI	NNH	P-value
Subject Report Of Scalp Irritation	Olsen[9] (2007)	5% minoxidil foam BID	6%	139%	3%	31	N/A
		Placebo	2%				
	Tsuboi[1] (2009)	5% minoxidil solution BID	N/A				
		1% minoxidil solution BID					
	Shin[3] (2007)	Placebo AM, 5% minoxidil solution / 0.01% tretinoin PM	31%	17%	4.6%	22	N/A
		5% minoxidil solution BID	27%				
Investigator Assessment Of Scalp Irritation	Olsen[9] (2007)	5% minoxidil foam BID	7%	-11%	-1%	-109	N/A
		Placebo	8%				
	Tsuboi[1] (2009)	5% minoxidil solution BID	8%	200%	5%	19	0.040
		1% minoxidil solution BID	3%				
	Shin[3] (2007)	Placebo AM, 5% minoxidil solution / 0.01% tretinoin PM	0%	-100%	-13%	-8	N/A
		5% minoxidil solution BID	13%				
Change in vital signs and/or abnormal labs	Olsen[9] (2007)	5% minoxidil foam BID	1%	-52%	-1%	-165	N/A
		Placebo	1%				
	Tsuboi[1] (2009)	5% minoxidil solution BID	1%	-33%	-1%	-150	N/A
		1% minoxidil solution BID	2%				
	Shin[3] (2007)	Placebo AM, 5% minoxidil solution / 0.01% tretinoin PM	N/A				
		5% minoxidil solution BID					

Based on investigator assessment, the Olsen study reported 7% of patients on 5% minoxidil foam BID to show at least a sign of scalp irritation versus 8% of patients on placebo

(Table 4). The corresponding NNH was calculated to be negative, with a value of -109, indicating that for every 109 patients treated with 5% minoxidil foam BID, one fewer patient would show signs of scalp irritations when compared to placebo (Table 4). The Tsuboi study reported 8% of patients on 5% minoxidil solution with at least one sign of scalp irritation versus 3% of those using 1% with NNH of 19 (Table 4). This was a significant finding considering the p-value of 0.040 (Table 4). The Shin study showed no patients having signs of scalp irritation on the combined product whereas 13% of patients on 5% minoxidil solution BID had signs of scalp irritation as examined by the investigators (Table 4). The corresponding NNH was -8 (Table 4).

As for systemic adverse effects, the Olsen study reported 1% (1/180) of patients on 5% minoxidil foam BID as well as 1% (2/172) of patients on placebo to have increased blood pressure and/or body weight (Table 4).[9] When these subjects had blood drawn for further investigations, serum minoxidil levels were within normal limits and well below the threshold for cardiac-related events.[9] Once the NNH was calculated, it was -165 (Table 4). The Tsuboi study reported 1% (2/150) of patients on 5% minoxidil solution and 2% (3/150) of patients on 1% minoxidil with abnormal lab values that included increased eosinophil count and increased total bilirubin (Table 4).[1] However, the study stated that the changes were mild with all subjects recovering without treatment, and specifically emphasized that there were no cardiac-related adverse events in either group.[1] The corresponding NNH was -150 (Table 4).

Discussion

In terms of efficacy, Table 2 shows the mean changes from baseline for all formulations of minoxidil exceeding the 4.7 for placebo. Table 2 data further suggests 5% minoxidil solution BID to be most efficacious based on having the highest change in hair count from baseline of 22.3. However, this number is not substantially different from the 20.9 for 5% minoxidil foam

BID, so the efficacy of 5% solution as compared to 5% foam is very comparable. Indeed an absolute conclusion cannot be made that solution is a better means of delivery given the disparity between the data for 5% minoxidil solution BID reported by the Shin study with a mean change in hair count of only 12.9 as opposed to 22.3 reported by the Tsuboi study. This discrepancy could be due to differences in study design. In the Tsuboi study, hair counting was recorded as the median count done blind on the monitor by five well-trained individuals.[1] In contrast, the Shin study used computer image analysis software to count the hair.[3]

Analysis of subject and expert assessment continues to support the efficacy of minoxidil in that there is a significant difference seen in improvement of hair growth going from placebo to 5% minoxidil foam BID given p-values <0.0001 with a NNT of five patients. Interestingly, looking at those with moderate improvement or better in hair growth, the NNT improved further to four based on subject assessment. The Tsuboi study also reported their results with the same granularity, with the expert assessment of moderate improvement in hair growth showing a significant p-value of 0.007 and corresponding NNT of eight, demonstrating that 5% minoxidil solution is more efficacious than the 1% minoxidil solution for patients seeking moderate improvement or better in hair growth, which one can assume most patients with AGA want.

Assessing the efficacy of foam versus solution delivery the subject and expert assessments cannot be used objectively to compare treatments across studies as presumably each study might have had different criteria for what a “slight” or “moderate” improvement was. Therefore, in light of the inconclusive results when comparing change in hair count numbers, it is not possible to determine whether foam or solution is a more efficacious means of delivery.

In terms of safety, subject report of symptoms of scalp irritation such as itching, burning, or stinging showed 6% (10/180) of patients in the 5% minoxidil foam BID versus 2% (4/172) in

the placebo group, yielding a NNH of 31 (Table 4). However, when expert assessment is also taken into consideration, one can see that there were more patients (8%) in the placebo group that reported symptoms versus 7% of patients in the 5% minoxidil foam BID, yielding a NNH of -109. This combined with the lack of systemic adverse effect establishes 5% minoxidil as safe.

As for determining the safer means of minoxidil delivery via foam or solution, the numbers for systemic adverse effects are inconclusive, showing equal percentages of patients in both groups (1%) experiencing some kind of change in vital signs and/or abnormal lab values (Table 4). In terms of minor side effects, such as scalp irritation, the numbers are fairly close under investigator assessment, but under subject report only 6% of patients for foam reported scalp irritation versus 27% of patients for solution (Table 4). Due to the subjective nature of the subject assessments, such data cannot be used conclusively to compare treatments across studies.

Conclusion

Based on this systematic review and the chosen studies, minoxidil is safe and efficacious in the treatment of male AGA especially at the optimal strength of 5% in either foam or solution preparation for twice daily use. The data within these three studies are consistent with the beneficial effects of minoxidil as well as its overall safety with no systemic adverse effects. Future studies should expand on the Shin study with a larger sample size to investigate the possibility of the combined product of 5% minoxidil/0.01% tretinoin. Since there is usually an inverse relationship between administration frequency and compliance with medication, this combined product would provide a good alternative in terms of increasing compliance as it only requires once daily application versus the twice daily minoxidil only treatments.[3] Another area that future studies can look into is a comparative assessment of minoxidil to finasteride as well as an investigation of possible synergistic benefits if combined in the treatment of male AGA.

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