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# The Effectiveness of Allogeneic Mesenchymal Stem Cells Therapy on Hair Regrowth in Androgenetic Alopecia: A Randomized, Double-Blind, Placebo Control Trial

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## Abstract

Objectives: The objectives of the study (i) to compare the mean hair regenerative effect of allogeneic bone marrow-derived MSCs versus Placebo, in treatment of AGA, (ii) to determine and compare the investigator's assessment and patient satisfaction in both groups.

Methodology: This randomized double-blind placebo-controlled trial was conducted at Dermatology department of National University of Medical Sciences in collaboration with Department of Cellular Therapy and Regeneration, National Institute of Blood and Marrow Transplant, Rawalpindi, Pakistan between January 2025 and June 2025. Of 131 patients screened, 120 eligible adult patients with clinically diagnosed AGA (Hamilton-Norwood II–VII) were randomized 1:1 using an online randomization tool to receive either a single intradermal injection of 2 million BM-MSCs (intervention group, n=60) or placebo (control group, n=60) into affected scalp areas. Twelve patients (6 in each group) were lost to follow-up; 108 participants completed the study and were included in the final analysis (n=54 per group; intention-to-treat). Blinding was maintained for both participants and investigators. Primary endpoints were changes from baseline in total hair count and hair diameter at 12 weeks, assessed via phototrichoscopy on a marked target area. Secondary outcomes included investigator-assessed global photographs and patient satisfaction (measured via a Likert scale).

Results: At 12 weeks, the BM-MSC group showed statistically significant improvements in both total hair count (mean difference; p<0.001) and hair diameter (mean difference; p<0.001) compared to the placebo group. Subjective patient satisfaction and investigator global assessment scores also improved significantly in the BM-MSC group (p<0.001). No serious adverse events were reported. Minor local side effects occurred in a few patients and resolved spontaneously.

Conclusions: Allogeneic BM-MSC therapy appears to be a safe and effective treatment for androgenetic alopecia, demonstrating significant improvements in hair count, diameter, and patient satisfaction at 12 weeks. These findings support further large-scale trials to confirm long-term efficacy.

Keywords: Androgenetic Alopecia, Alopecia, Mesenchymal Stem Cells, Bone Marrow, Allogeneic Cells, Hair, Hair Follicle, Hair Loss, Hair Regeneration

## Introduction

Androgenetic Alopecia (AGA) is a common form of hair loss affecting both genders worldwide[1], characterized by the miniaturization of hair follicles due to factors including androgens and genetics. While many accept it as a normal physiological process of ageing, for others it causes remarkable worry, especially pertaining to personal appearance and self-confidence. Current treatment options, such as minoxidil, finasteride, hair transplant and platelet rich plasma (PRP) therapy, have limitations in efficacy and number of adverse effects.[2,3] Stem cells have emerged as a potential treatment option owing to their regenerative, immunomodulatory, homeostatic and tissue remodeling properties.[1,2,4,5,6]

Cellular and cell derived therapies such as PRP, injectable platelet rich fibrin, adipose derived stem cells, hair follicle progenitors, and exosomes are being investigated for AGA, though evidence is heterogeneous and standardized protocols are lacking. In this context, bone marrow derived mesenchymal stem cells (BM-MSCs) represent a novel therapeutic avenue. Stem cell transplantation therapy can be either autologous (self) or allogeneic (matched or unmatched donor).[1] Stem cells

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are classified into adult and perinatal groups. Adult stem cells include those derived from adipose tissue (ADSCs), hair follicles (HFSCs), and bone marrow (BMSCs). ADSCs are further classified into nano fat and stromal vascular fraction (SVF). Perinatal stem cells are sourced from the umbilical cord including Mesenchymal stem cells (MSCs) from Wharton's jelly, amniotic fluid, and placenta.[7] Based on origin and differentiation potential, adult stem cells are broadly categorized into hematopoietic stem cells, which give rise to blood lineages, and Mesenchymal stem cells (MSCs), which differentiate into mesodermal tissues such as bone, cartilage, and fat.[5,6]

Mesenchymal stem cells (MSCs) have been successfully used in over 200 clinical trials for conditions such as diabetes mellitus, systemic lupus erythematosus, scleroderma, cardiomyopathy, cirrhosis, osteoarthritis, and spinal cord injuries, in addition to their therapeutic applications in dermatology for chronic wounds, skin aging, psoriasis, atopic dermatitis, pemphigus vulgaris, vitiligo, and epidermolysis bullosa.[1,3,4,6,8] Stem cells are known to play a crucial role in initiating and promoting the hair growth cycle and remodeling. Emerging evidence suggests that stem cells may be responsible for releasing cytokines, chemokines, and specific growth factors like bFGF, VEGF, IGF-1, HGF, and TGF-β1.[8,9,18] These molecules initiate cell repair processes through angiogenesis, immunomodulation, cell differentiation, and proliferation. In the scalp, they exert a paracrine effect on neighboring cells and tissues, promoting hair follicle growth, adjusting hair growth patterns, regulating follicle size via angiogenesis, and supporting the retention of the anagen phase.[10-12]

MSCs are conventionally derived from bone marrow. Intradermal injection of BM-MSCs induced genes for hair regeneration and supported progression from telogen phase to anagen phase of hair growth cycle in various animal studies.[7] Anabolic and anti-inflammatory growth factors like PDGF, TGF-β, BMP-2 and 7 are concentrated in bone marrow aspirate concentrate[7] Human studies on BM-MSC for AGA are rare and need further research for clinical application.

Based on above evidence, there is a vast avenue of research in potential role of stem cells therapy in AGA, as an emerging approach.[13-15] A single trial of autologous bone marrow derived MSCs (BM-MSCs) therapy in AGA showed promising results, however no study exploring the therapeutic potential of allogeneic BM-MSCs in AGA has been done so far world over. So, we decided to explore the role of this novel treatment modality and conducted this trial as a pilot study to assess the efficacy and safety of intradermal injection of allogeneic BM-MSCs in our population of male patients with AGA. We hypothesized that MSCs therapy is superior than placebo for hair regeneration in treatment of AGA.

## Methodology

It was a randomized double-blind placebo-controlled trial from ClinicalTrials.gov NCT06764329; first posted January 8, 2025, approved by the ethical review committees at both institutes; (A/28/ERC/83/24 dated 20th June 2024) and (IRB-014/BMTC/Approval/2024 dated 10th July 2024), registered with ClinicalTrials.gov (ID NCT06764329) conducted between January 2025 to June 2025. The participants were enrolled in the study on voluntary basis from patients reporting to Dermatology outpatient department for treatment of AGA. Written informed consent was taken from all participants prior to enrollment.

Initial visit included eligibility screening of the participants.

All male patients with AGA between 20 to 59 years of age, with clinical presentation consistent with grade II to VII using Hamilton Norwood criteria were included in the study whereas exclusions from the study were made on following criteria: (a) all patients with hair loss other than AGA; (b) patients receiving antiandrogen or minoxidil therapy; (c) PRP at least 6 months prior to enrollment; (d) history of hypertrophic scars or bleeding disorders; and (e) history of hyper or hypothyroidism.

Screening involved 131 patients with 120 ultimately enrolled. Participants (n=120) were randomized post baseline measurements to either intervention group (IG; n= 60) receiving BM-MSCs or control group (CG; n=60) receiving the placebo (normal saline) by using clinical trial randomization tool available online (https://ctrandomization.cancer.gov/). The investigators involved in enrollment, procedure and outcome measurements were blinded to randomization process.

Each participant in the intervention group received allogeneic BM-MSCs at a total dose of 2 million cells

(1million/ml) in the affected area of scalp through intradermal injection. BM-MSCs were expanded *ex-vivo*, following the previously published culturing protocol.[16,17] A brief summary of which is given below:

Bone marrow harvest: After obtaining informed written consent, MSCs were derived from bone marrow samples harvested (BMH), 50ml/each healthy volunteer donor under aseptic conditions through general anesthesia. Necessary infectious screening of all donors including Human Immunodeficiency virus, Hepatitis B and C, Epstein Barr virus human T cell lymphotropic virus, and cytomegalovirus was carried out.

Mononuclear cell (MNC) isolation from BMH: BMH sample was mixed with phosphate buffered saline (PBS) in equal ratio and layered on Ficoll density gradient solution (1.077g/L). After centrifugation, the sample separated in 3 layers. 2nd layer of mononuclear cells was (MNCs) pipetted and washed with PBS yielding a pellet of MNCs.

Seeding of MNCs and culturing of MSCs: Single cell suspension of MNC pallet was loaded in 5 x 175 $cm^2$ culture flasks. Cells were cultured in 27 ml Dulbecco's Modified Eagle Medium (DMEM) and 3ml of sterile pooled human platelet lysate (hPL) as a source of growth factors. Growth medium was changed every 3 days until cells were nearly 90% confluent. Identity of MSCs was confirmed through phase-contrast microscopy.

Dissociation of MSCs: MSCs were detached from the culture flasks by adding 1% trypsin enzyme. The enzymatic activity of trypsin was stopped with PBS/DMEM and centrifuged yielding single cell suspension of the pallet, containing MSCs ($P_0$).

*Ex-vivo* Expansion of MSCs: $P_0$ cells were seeded again at low density and cultured to new passage in more flasks until a total yield of about 100 million MSCs was achieved from 50 ml BMH.

Aliquoting and cryopreservation of MSCs: For alopecia patients, MSCs were aliquoted in doses of 2 million cells in cryovials which were cryopreserved in 10% DMSO, 45% DMEM and 45% hPL and stored at -80$^o$C. At time of issue, each dose was reconstituted in 2 ml saline and was dispensed in 2 insulin syringes each containing 1 million cells/ml.

Prefilled insulin syringes labelled with patient specific numbers were provided by laboratory staff at the time of procedure. Cold chain was maintained while transfer from stem cell lab to the Dermatology clinic of the hospital. Doses were injected within one hour of thawing. Patient's scalp was sterilized with alcohol swabs prior to procedure. To provide pain relief, vibration devices were used locally during the procedure. Each candidate received 2 ml dose of colorless fluid injected intradermally at an angle of 30° to cover an area of approximately 1$cm^2$ with each prick; under aseptic measures.

To determine the safety, vital signs were recorded before and 30 minutes after the procedure. Patients were observed for any immediate reactions for one hour after the procedure. Feedback was also taken from the participants regarding any possible side effects like excessive pain, itching, burning, headache, rash or any other adverse event.

Primary efficacy variables included change from the baseline in total hair count (HC) and the hair diameter (HD) assessed through phototrichoscopic analysis at baseline and 12 weeks post-intervention, performed on same area on scalp marked by tattoo spot. The Secondary outcome measures included investigator's assessment through photographs of patients' scalp pre- and post-intervention, as well as subjective satisfaction reported by the patient.

Investigator assessment was based on the photography of four standard views of patients scalp at baseline and 12 weeks post treatment. (Figure 1,2) Pictures were taken from four standard views including hair line from front and both sides (45) as well as vertex (90) for each patient. Photographs were obtained using a high quality DSLR camera (Nikon D-5300) with maximum effort to standardize the photography conditions. A blinded investigator assessed changes in hair appearance from baseline using a 5-point rating scale.

At 12 weeks post treatment participants performed self-assessment regarding improvement in hair fall as well as new hair growth, both based on a 4-point Likert scale.

Sample size was calculated by using OpenEpi Sample size calculator based on work by Tak YJ *et al*.[18], who tested the efficacy of adipose-derived stem cell constituent extract in AGA. Total sample size was 70 with

35 patients in each group with significance level 5%. Power was 80%. Data was analyzed using IBM SPSS 25.0. Mean and standard deviation were calculated for

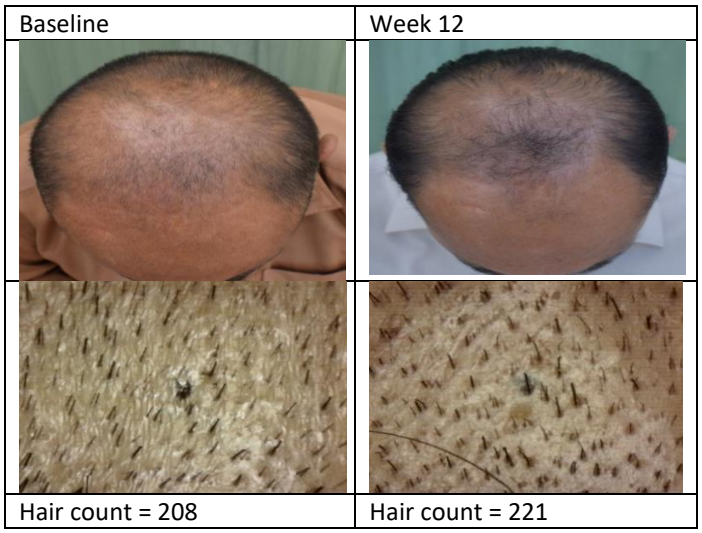



Fig 1 a

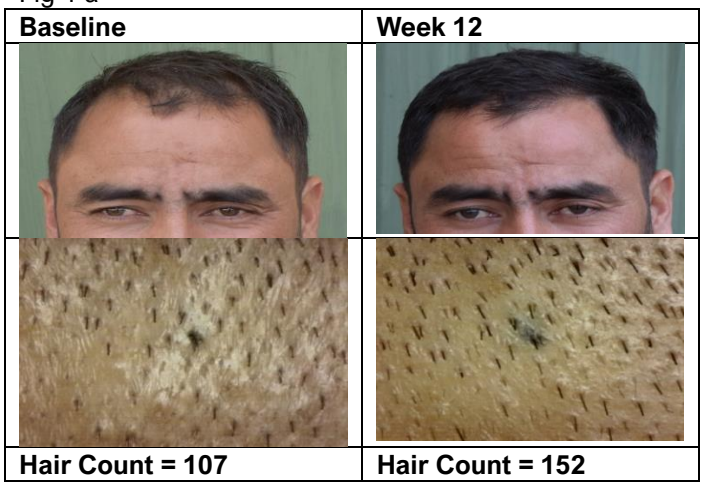



Fig 1 b

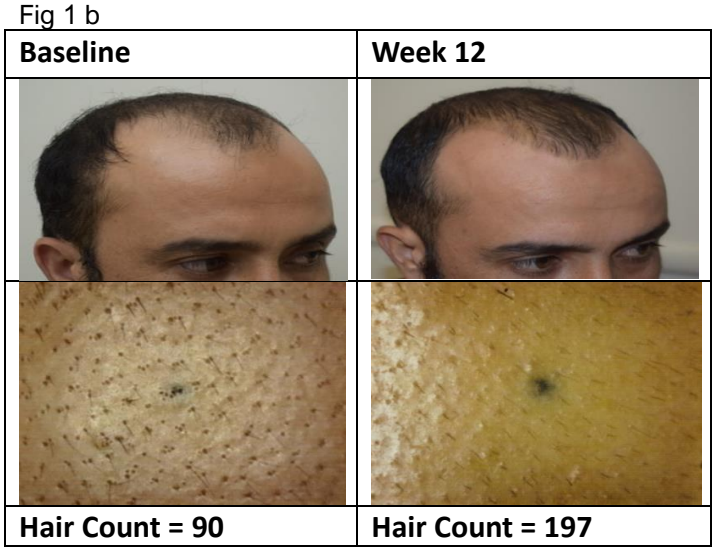



Fig 1c

**Figure 1 (a,b,c) : Scalp photography with phototrichoscopic images comparison.**

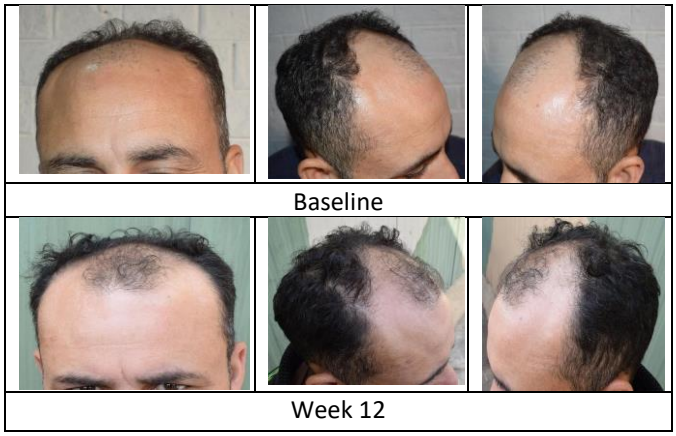



**Figure 2. Baseline and 12 weeks post intervention comparisons in IG.**

quantitative variables like age, hair count and hair density. The paired T test was used to compare two separate groups for hair count and hair diameter before and after treatment. Chi-square testing and Mann Whitney U tests were used for the ordinal variables like investigator assessment and patient satisfaction as they were checked on Likert scale.[19] A p-value of ≤ 0.05 was regarded as statistically significant.

## Results

Initially 120 patients were enrolled in the study however 12 patients were lost to follow up (IG = 6, CG = 6) and total 108 patients completed the trial. Comparison of baseline characteristics between two groups showed no significant inter-group differences in the demographic, anthropometric characteristics and smoking habits indicating appropriate random assignment. Overall mean age of participants of study was 36.68 ±7.1 years (range: 21-55 years). In CG mean age was 36.61 ± 7.8 years and in IG it was 36.74±6.5 years ($p$=0.926).

Following minor self-limiting side-effects were recorded. (graph 1) In addition to the primary outcomes, we observed several unexpected effects, which warrant further research. (graph 2)

## Discussion

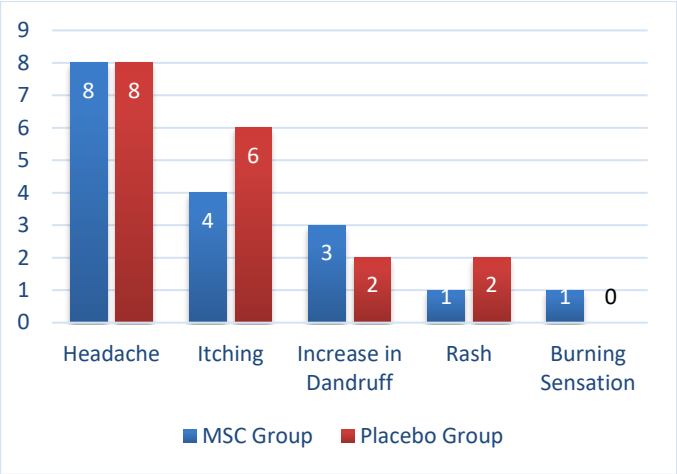
Stem cell therapy, owing to its regenerative and immunomodulatory properties, has attracted growing interest as a potential treatment for AGA. Several randomized controlled trials have been conducted to

| Table I : comparison of patients' demographics and study outcomes between IG and CG. | | | | |
|---|---|---|---|---|
| 1. Hamilton Norwood Scale of AGA | | | | |
| Stage | IG (n= 54) MSC | CG (n=54) Placebo | | p-value |
| 2 27 (25%) | 15 | 12 | | 0.823 |
| 3 44 (40.7%) | 20 | 24 | | |
| 4 14(13%) | 8 | 6 | | |
| 5 12 (11.1%) | 5 | 7 | | |
| 6 6 (5.6%) | 4 | 2 | | |
| 7 5 (4.6%) | 2 | 3 | | |
| 2. Smoking status | | | | |
| Smoker 36 (33.3%) | 17 | 19 | | 0.683 |
| Non-smoker 72 (66.6%) | 37 | 35 | | |
| 3. Objective assessment of Hair Count before and after treatment | | | | |
| Before Intervention | 150.3 ±59.7 | p-value | 165.6±58.3 | p-value |
| After Intervention | 159.3±58.3 | <0.001 | 163.7±56.8 | 0.412 |
| 4. Objective assessment of Hair Diameter before and after treatment | | | | |
| Before Intervention | 58.9±9.3 | p-value | 58.1±8.5 | p-value |
| After Intervention | 60.27±10.38 | <0.001 | 58.1±9.3 | 0.922 |
| 5. Investigator Assessment via photographs (pre and post intervention) | | | | |
| Slightly decreased 01 (0.9%) | 01 | 0 | | 0.001 |
| Unchanged 60 (55.6%) | 21 | 39 | | |
| Slightly increased 26 (24.1%) | 15 | 11 | | |
| Moderately increased 16 (14.8%) | 12 | 4 | | |
| Greatly increased 05 (4.6%) | 5 | 0 | | |
| 6. Patient satisfaction with Hair Regrowth | | | | |
| 1- Some Hair loss 10 (9.25%) | 2 | 8 | | <0.001 |
| 2-No new hair regrowth 14 (12.96%) | 1 | 13 | | |
| 3-Some new hair regrowth 58 (53.7%) | 32 | 26 | | |
| 4-A lot of new hair regrowth 26(24%) | 19 | 07 | | |
| 7. Patient satisfaction with improvement in Hair fall | | | | |
| Unsatisfied 16(14.8%) | 3 | 13 | | <0.001 |
| Neutral 27(25%) | 5 | 22 | | |
| Satisfied but having some hair fall 28(25.9%) | 20 | 08 | | |
| Very Satisfied (no hair fall) 37(34.2%) | 26 | 11 | | |
| 8. Side-effects | | | | |
| Headache 16 (14.8%) | 8 | 8 | | 0.753 |
| Itching 10 (9.25%) | 4 | 6 | | |
| Increase in Dandruff 05(4.6%) | 3 | 2 | | |
| Rash 03 (2.7%) | 1 | 2 | | |
| Burning sensation 01 (0.9%) | 1 | 0 | | |
| 9. Other Positive effects noticed by the patients | | | | |
| Decrease in dandruff 10(9.25%) | 4 | 6 | | 0.152 |
| Re-pigmentation of hair 02(1.85%) | 2 | 0 | | |
| Improved Hair texture 11(10.18%) | 8 | 3 | | |

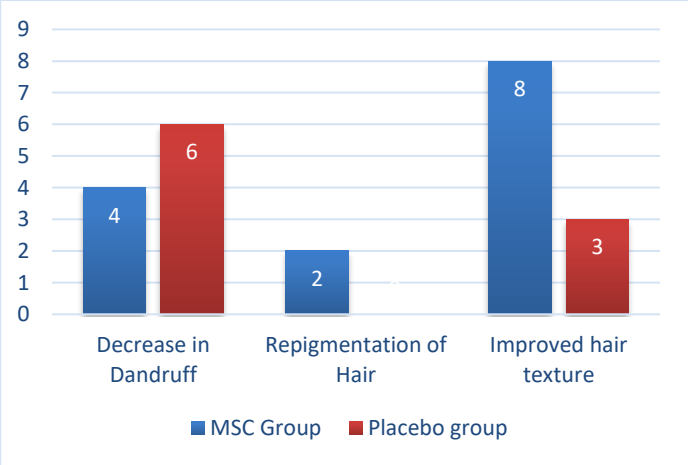
date evaluating the efficacy of stem cells and their derivatives isolated from different sources i.e., Adipose tissue of the patient, their hair follicles, autologous bone marrow cells, umbilical cord blood cells and exfoliated deciduous teeth.[20] Our study is a pilot study exploring the hair regenerative properties of allogenic bone marrow derived stem cells in androgenetic alopecia.

One hundred and eight male patients completed our study with age range of 21-55 years. Tak *et al* conducted RCT on 38 patients of AGA utilizing ADSCs the age range was 18-59 years.[18] Elmaadawi *et al* compared the efficacy of autologous bone-marrow derived stem cells vs follicular stem cells in resistant cases of AGA and Alopecia Areata, age range was 10-50 years with sample

size of 20 in total.[21] Our trial included a larger number of participants compared to most previous studies, which strengthens the reliability of our preliminary observations.




Graph 1: Comparison of side effect profile.




Graph 2: Incidental observations.

We have used the Hamilton Norwood scale for grading AGA in our study with 25% patients having stage 2, 40.7% stage 3, 13% stage 4, 11.1% stage 5, 5.6% stage 6 and 4.6% stage 7 of AGA. It was comparable to the findings of another study carried out by Legiawati et al in Indonesia exploring the combination of ADSC with minoxidil in 37 patients of AGA, in which 8.1% patients were of Hamilton Norwood stage 3, 10.8% were of stage 3 vertex, 10.8% stage 4, 21.6% stage 4a,10.8 % stage 5, 13.5% stage 5a, 24.3% stage 6.[22] In a South Korean study BASP classification was used combining the patterns of anterior hair lines i.e., L, M, C and with density of hair follicles in frontal and vertex areas. Subjects included were at least M2, C2, U1 basic types and V1 and F1 specific types.[18]

In our study 33.3% patients were smokers (15.7% IG vs 17.6% CG) and 66.6% were nonsmokers (34.2% IG vs 32.4% CG). In study by Legiawati *et al*, 24.3% were smokers with 13.5% in one group and 10.8% in the other group.[22] In the study by Tak *et al*, 11.76% participants were smokers out of which half were in IG and half in CG.[18]

Side-effects noted in our study were headache (14.8%), itching (9.25%), increase in dandruff (4.6%), rash (2.7%) and burning sensation at injection site (0.9%). (Graph 1) The difference between two groups was not statistically significant i.e.,0.753. Gan *et al* evaluated the efficacy of autologous HF-MSC therapy in AGA. The side effects noted were: redness (2%), swelling (4%), pruritus (2%) and erythroses (2%).[23] In another study using ADSC in AGA seven mild side-effects were noted in 5 patients which resolved on their own. There was no intergroup difference in incidence of these side effects.[18] Tolerable and self-resolving side-effects were noted i.e. pain, itching and redness in the injection sites in another study using stem cells.[22] Allogeneic MSCs are considered relatively hypoimmunogenic, which reduces the risk of graft-versus-host disease (GVHD).[24]

Hair diameter (HD) and hair count (HC) were objective assessment parameters in our study. In the MSC group the difference in the HC in the treated area was significant i.e. <0.001 and was insignificant for the placebo group i.e. 0.412. Similarly, the HD improvement before and after in IG was significant i.e. <0.001 and was insignificant for CG i.e. 0.922. In study by Legiawati *et al* HC, HD, vellus rate, terminal rate, mean thickness and total follicular units (TFU) were the assessed parameters. In both the groups these parameters improved over 6 weeks but there was no significant intergroup difference. Changes before to after treatment in both groups were statistically significant ($p<0.05$). In contrast a dramatic decrease of TFU was noted in the CG ($p=0.005$)[22] In another study utilizing ADSC in AGA there was a significant improvement in HC (28% vs 7.1%) and HD (14.2% vs 6.3%) in IG versus the CG.[18] Gan *et al* compared mean hair diameter, proportion of terminal hair, cumulative hair diameter and follicular units/cm2 in two groups; hair follicle derived MSCs versus placebo in AGA. No significant intergroup differences were observed.[23]

In our study 34.7% of patients reported being very satisfied with the improvement in the hair fall with 24% in IG and 10% in the CG. 14.8% were unsatisfied with 2.7% in the IG and 12.1% were in the CG. The difference between the two groups was statistically significant i.e., <0.001. 24% experienced hair regrowth in the form of a lot of new regrowth (17.6% in IG vs 6.48% in CG) with significant difference between the two groups i.e., <0.001. 9.25% patients experienced hair fall (1.85% in IG vs 7.4% in CG). Legiawati et al assessed patient satisfaction at 5-point Likert scale after ADSC treatment for AGA. 81.08% patients were very satisfied and 18.9% were satisfied with the final outcome.[22]

In summary, our study observed significant within-group improvements in HC, HD, investigator assessment, and patient-reported satisfaction in the allogeneic MSC group compared to placebo. These findings suggest that BM-MSCs may hold therapeutic potential for AGA. However, given that this was a pilot study with a single session, relatively short follow-up, and limited geographic recruitment, the results should be interpreted with caution. Larger multicenter trials with longer follow-up are required to confirm these preliminary findings.

Two of our patients in the MSCs group developed repigmentation of graying hair (Graph 2). This is a new finding and supports the pathogenesis of hair de-pigmentation. The root cause of graying is the loss of melanocyte stem cells (McSCs) in hair follicle pigment unit (HFPU). As individuals age, dormant melanocyte stem cells (McSCs) accumulate in the hair bulb without contributing to new melanocyte production. These preserved McSCs are crucial to the reconstruction of HFPU and provide the possibility of repigmentation of gray hair. Once they are lost, this hope vanishes.[25] This incidental observation raises the hypothesis that our therapy might have influenced these dormant cells, potentially contributing to repigmentation, though this remains speculative and requires confirmation in dedicated studies.

Limitations: This trial has several limitations. First, objective assessment of HC and HD was performed at a single frontal site, whereas photographic analysis suggested improvement in other scalp regions that were not quantified. Future studies should incorporate multi-site objective assessments, though this may pose cosmetic challenges for participants. Second, phototrichogram analysis was performed manually using open-source software due to resource constraints; automated standardized software would provide greater accuracy. Third, the study was conducted at a single center, which may limit generalizability. Finally, the design included only a single low-dose session with 12-week follow-up, which is relatively short for a regenerative therapy trial. Longer studies with repeated dosing are warranted to fully assess both safety and sustained efficacy.

Strengths: Despite these limitations, this trial has several strengths. To our knowledge, it is the first randomized, double-blind, placebo-controlled clinical trial to investigate the use of allogeneic bone marrow–derived MSCs in AGA. The sample size was larger than many previously published stem cell studies in hair disorders, which provides supportive evidence. Both objective parameters (HC and HD) and subjective assessments (patient satisfaction and investigator evaluation) were used, providing a comprehensive assessment of outcomes. Furthermore, the use of allogeneic cells circumvents the need for invasive harvesting procedures, supporting the feasibility of this approach for wider clinical application.

## Conclusion

Within the limitations of this pilot randomized trial, allogeneic BM-MSC transplantation appeared safe and showed encouraging signals of efficacy in AGA. While our results support further exploration of this novel treatment modality, definitive conclusions about its effectiveness cannot yet be drawn. Future studies with multiple sessions, higher dosing, and longer-term follow-up are needed to fully establish its clinical value.

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