INFORMATION BRIEF (RAPID REVIEW)

Autologous Cellular Micrograft *(Regenera Activa)* for treatment of Androgenic Alopecia

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
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TITLE: AUTOLOGOUS CELLULAR MICROGRAFT *(REGENERA ACTIVA)* FOR TREATMENT OF ANDROGENIC ALOPECIA

PURPOSE

To provide brief information on the effectiveness and safety of Autologous Cellular Micrograft *(Regenera Activa)* for treatment of Androgenic Alopecia following request from the Director of Medical Practice Division, Ministry of Health, Malaysia.

BACKGROUND

Androgenic alopecia (AGA) is the common cause of non-scarring alopecia in both men and women. In an observational study conducted by Ng KF.et.al (2017) reported that in Malaysia, AGA is the most prevalent type of alopecia. The most common ethnic affected by this condition are Malays (42.1%), followed by Indians (26.3%), Chinese (26.3%) and others (5.3%).[1] The illness usually manifests itself through increasing hair loss that follows a pattern. It can start at any age after puberty, however the incidence increases with ages. Up to 42% of women and 80% of men will exhibit AGA characteristics by the time they are 70 years old and older.[2] Reduced hair density and shrinking of hair follicles in the affected scalp area are observed in patients with AGA. In this disease entity, the length of terminal hair growth gradually decreases.[3] Androgenic alopecia is a complex disorder of multifactorial origin, in which genetics plays an important role. In males, it is an androgen-dependent feature since the terminal follicle becomes susceptible to Dihydrotestosterone (DHT), shortening the anagen phase; whereas in women, the associated hormonal mechanisms are less evident.[4]

Hair follicles are complex structures that go through several biological phases, including the anagen, phase of active growth, the catagen, an intermediate remodeling phase, and the telogen phase, which is a time of quiescence.[4] The pathogenesis of Androgenic alopecia is characterized by a shortening of the anagen phase and an increase in the amount of hair follicles that remain in the telogen phase. Since the anagen phase determines hair's length, the new hair in AGA is shorter, gradually miniaturizing hair follicles until they disappear.[5,6] In male pattern AGA, a receding front line, mainly triangular in shape, is seen, followed by thinning at the vertex area.[7] Female pattern AGA is characterized by diffuse thinning of the central-parietal region and preservation of hair front line.[2] The hair of the human scalp plays an important role in determining one’s appearance and is an important sociocultural role. Hairstyles and lengths are distinctive features of an individual’s identity, and hair loss can have a negative impact on self-esteem and cause women in particular tend to dissatisfied with their looks. Nevertheless, hair loss is also associated with psychological and social difficulties in men.[8,9]

There are few available therapies for AGA. The only FDA-approved treatment for females is topical minoxidil, whereas the only FDA-approved treatment for males is topical minoxidil plus oral finasteride 1 mg. Studies indicated that only one-third of patients have a cosmetic benefit or moderate terminal hair regrowth after using minoxidil for a year due to its low efficacy.

Topical minoxidil use is frequently associated with erythema, hypertrichosis, increased seborrhea, and scalp irritation. In view of its teratogenicity, the FDA has approved oral finasteride 1 mg for male AGA but not for female AGA. About 3 - 5% of men taking finasteride have reported experiencing decreased libido, erectile dysfunction, and ejaculatory issues. Furthermore, minoxidil and finasteride demand a daily, long-term commitment from the patient on a daily basis, most likely for lifelong. Hair transplantation may be the only choice for some individuals with advanced stages of pattern hair loss (PHL) however effectiveness varies depending on the surgeon techniques. There is limited donor supply for many balding males to cover the bald area. A lot of female PHL patients have weak donor areas and are not good candidates for hair transplants. [10] Some cosmetic techniques like platelets Rich plasma (PRP) and low -level laser/led light therapy (LLLT) had been introduced as a treatment of Female-AGA, however its effectiveness is uncertain.[11]

Recently increasing interest has been shown on Autologous Cellular Micrograft *(Regenera Activa)* as one of the cutting edge therapies for hair loss. It is claimed to be an innovative, simple and effective regenerative method to obtain Autologous micrografts using Regenera technology.[11] This one-time procedure is intended to help stimulate hair growth and delay the progression of hair loss. Autologous Cellular Micrograft is relatively safe and was found to be painless sampling procedure after local anaesthesia injection. This procedure is done by collecting stem cells from the patients without using any chemical during the treatment. It can be carried out comfortably in the clinic and it only takes about 30 to 45 minutes.[11] The foundation of this non-surgical procedure is stimulating self regeneration by activating native progenitor cells located in the homologous tissues, through a simple process, without risks to the patient and great therapeutic potential.[11] Autologous Micrograft Technology (AMT) obtains injectable micrografts composed of cells (stem cells and progenitor cells), extracellular matrix, and growth factors derived from the patient's own cells, with no other manipulation than mechanical aggregation. This technique is based on clinical studies showing a high concentration of the cells obtained from solid tissues. The hair micrografts will be injected into the follicles surrounding balding spots. In a single session, the patient is a donor and recipient of autologous micrografts, allowing the recipient area to benefit from the regenerative activity of the progenitor cells and growth factors extracted from the donor site.[11]

Figure 1 : ACM Procedure using Rigeneracons class 1 medical device

EVIDENCE SUMMARY

A total of 50 titles were retrieved from the scientific databases via OVID, PubMed and general search engines [Google Scholar], using the search term; *androgenic alopecia, female/male pattern baldness, autologous cellular micrograft* and *regenera activa.* The last search was conducted on 22nd April 2024. The articles were found to be relevant and included in this review which comprised of interventional studies (six).

EFFICACY/ EFFECTIVENESS

Katarzyna. K et al (2024) conducted an interventional study aimed to evaluate the effectiveness of Autologous Cell Micrograft (ACM) in improving the AGA in women after 6 months single injection of ACM. This interventional study involved 23 female patients from one centre who were clinically and dermoscopycally confirmed to have been diagnosed with AGA grades one to three, according to Ludwig scale. In order to evaluate the hair growth post treatment with ACM, pictures of patient's scalps were taken before and six months after the treatment session. The pre and post treatment photos were taken with the patients in the same head position in the same room with comparable lighting. Using the Visual Analogue Scale (VAS) scale, four dermatology specialists independently assessed the pictures taken before and after the treatment to assess its efficacy. The review reported after ACM with Regenera Activa treatment, there was an average increase of VAS score by 1.5 points and average improvement of 1 degree on the Ludwig scale. [12]

Mei WC et al. (2023) conducted an interventional study to evaluate the efficacy of Autologous Cellular Micrografts (ACM) in AGA. This study involved a total of 25 male and female patients diagnosed with AGA from the age of 23 years to the age of 64 years. The results showed an increase in the total number of hairs per centimeter from the scalp and hair density. An analysis of the effects of ACM treatment on hair was done using a Paired Samples T-test for androgenic alopecia (AGA). All hair parameters, including hair count (+41.56 hair/cm^2), hair density (+27.09 hair/cm^2), anagen (+5.89%), telogen (+6.55%), density of vellus hair (5.43 hair/cm^2), density of terminal hair (19.16 hair/cm^2), ratio of vellus hair (3.29%), and ratio of terminal hair (4.29%), showed a significant increase, according to the results. Values before and after the intervention had a moderate to significant correlation (r = 0.548 to 0.840). The mean change in hair density was greater in females than in males (p = 0.034). Males, however, had a larger density terminal mean change than females (p = 0.031). Telogen mean change was substantially correlated with age; patients over 35 had a considerably higher Telogen mean change (6.10 ± 0.93) than patients 35 years of age or younger (p-value = 0.019). As a result, there was an increase in the average of total hair count 41.56 hairs/cm^2 of each 1cm^2 scalp. Moreover, the average of hair density increase is 27.09 hairs/$cm^{2.}$ The changes in hair density and total hair count varies from patient to patient. Some cases showed changes as early as one month post intervention, however some cases take 6 months.[11]

Alvarez X et al. (2018) conducted an interventional study involving 17 patients that were randomly recruited and treated with Rigenera ® system. Based on macroscopic and microscopic photographic evaluation study, four patients (23.53%) had improved hair density, 13 patients (76.47%) reported no change, and none of them reported a decline in hair density. Concerning the subjective evaluation of patient satisfaction, out of the 17 patients who received treatment, one patient reported being extremely satisfied (5.88%), five reported being fairly satisfied (29.41%), eight reported being satisfied (47.05%), one reported being slightly satisfied (5.88%), and two reported being unsatisfied (11.76%). As for patient's perception of change in hair thickness, 12 patients (70.58%) noted an increase in thickness, while five patients (29.41%) documented no changes at all. Regarding patients' assessment of change in hair loss according to Hair Loss Test, eight patients (47.05%) reported a decrease in hair loss whereas nine patients (52.94%) did not perceive any difference.[13]

Ruiz RG et al. (2019) conducted an interventional study to assess the efficacy of the progenitor-cell-enriched micrograft at four,six and 12 months, among 100 patients that were clinically diagnosed with AGA upon presentation. The results showed a significant improvement in hair density (+33.3/cm^2) and percentage of thick hair (+5.6%) at two months. Photograph and TrichoScan® analysis was used to confirm the visual result. Mallory's trichrome staining was used to perform histological evaluations on scalp biopsies at baseline, six and nine months following the implantation of micrografts. The number of hair follicles increased six months after the administration of micrografts, with the initiation of cuticle production and dermal papilla growth. A well-organised dermis, more regular and structured collagen fibers, hair follicles in the Anagen IV/Mesanagen phase were observed after nine months. Additionally, thick dermal papilla and indications of cell growth also noticed.[14]

Gentile et al. (2017) conducted an interventional study involving 11 patients from 38 to 61 years of age affected by AGA in stage three to stage five according to Norwood-Hamilton classification scale. In this study, human follicle stem cells (HFSCs) taken using mechanical centrifugation of punch biopsy were used to improve hair density in all the patients. All patient

were evaluated in four phases: T0, the start of the study, T1 in three weeks, T2, in nine weeks; T3, in 16 weeks, and T4, in 23 weeks following the last treatment. In particular, the result showed 29% ± 5% increase in hair density in the treated area at the 23-week follow-up, compared to less than 1% in the placebo area.[15]

Zari S et al. (2021) conducted an interventional study to evaluate short-term efficacy of single application Autologous Cellular Micrografts in male and female patients with AGA. The review involved 140 consecutive adults with confirmed AGA, who received a single session of ACM (Regenera Activa®). Using TrichoScan digital image analysis, the effectiveness of a single application of ACM was assessed one to six months after treatment by examining changes in trichometry parameters. Improvements were observed in all positive parameters, ranging from hair density (+4.5 to 7.12 hair/cm^2), Average Hair Shaft Thickness (AHST) (+0.96 to 1.88 µm), percentage of thick hair (+1.74 to 3.26%), Cumulative Hair Thickness (CHT) (+0.48 to 0.56 unit), and number of follicular units (+1.30 to 2.77), with the most notable improvements in the frontal region where all changes were statistically significant ($p < 0.05$). The frontal region showed a significant decrease in negative characteristics, namely in yellow dot (-1.93 N/cm^2, $p = 0.003$) and thin hair (-1.81%, $p = 0.037$). Pre- and post-intervention values were associated moderately ($r = 0.5390.8$) in most parameters.[10] They found, for males, the most notable outcome was a rise in hair density, whereas females had an increase in hair thickness and a decrease in the quantity of yellow spots. Women show a significant improvement in all hair growth indicators in the occipital region with a single ACM session, despite the fact that none of the study patients received treatment in this area. This finding may have implications for improving the donor area in females who require hair transplantation.[10]

Favorable changes were observed in all positive and negative trichometry parameters between the pre- and post-intervention assessments. These included an average of five to seven new hairs growing per cm^2 of scalp and an increase in average hair thickness of 1.6 to 1.9µm, which is represented by a proportionate decrease in the percentage of thin hairs and an increase in the percentage of thick hairs. There was a noticeable one to two yellow dot reduction per cm^2 of scalp along with a 3% increase in the percentage of follicular units. All of these changes corresponded to an average improvement in the CHT of 0.5 to 0.6 units, or a 5 to 6 mm^2 increase in the hair coverage index per cm^2 of scalp. This produced a notable cosmetic benefit, as the author's visual model for this study shows. Depending on the measure, such good results were seen in as many as two thirds of patients. The magnitude of alterations among positive responders was more notable, particularly in the frontal region. These results, which show several short-term benefits of ACM in enhancing AGA patients' hair, are very promising.[10]

SAFETY

[redacted] medical device obtained Conformité Européenne (CE) approval (class 1; Human Brain Wave, Turin, Italy).[10,12,14]

Mei WC et.al (2023) in their interventional study, reported no side effects in any of the patients following ACM. This method maintains a high level of safety, and while its effect are not immediate. The incision made during the hair follicle extraction procedure are small,

measuring about 3 to 4 cm in diameter, and they healed within four to seven days. After treatment, patients can resume their regular lives right away because there is essentially no downtime. [11]

COST/COST-EFFECTIVENESS (If any)

There was no retrievable evidence from the scientific databases on the cost/cost-effectiveness of Regenera Activa in treatment Androgenic Alopecia.

Estimated cost for Regenera Activa treatment in India was is USD 2.3 thousand per session.[16] The cost for this procedure in Europe is about USD 1.3 to 1.9 thousand per session and the session must be repeated every year or every 2 years.[17] The cost per session of Regenera Activa in Singapore is about USD 2.2 thousand.[18]

CONCLUSION

Based on the review, the evidence showed potential benefit of Autologous Cellular Micrograft *(Regenera Activa)* in the treatment of Androgenic Alopecia. The evidence demonstrated this procedure is moderately effective in increasing hair count and hair density and safe for treatment of Androgenetic Alopecia involving studies with sample range from 11 to 140 patients with longest follow up up to one year. Further research may be conducted to ascertain its effectiveness in longer term.

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