

Stem cell secretome-mediated alleviation of scalp psoriasis: A case report

Anjum Mahmood¹, Naman Somani¹, Divyang Patel¹, Rangnath Mishra^{1,2}, Anand Srivastva^{1,2,*}

¹GIOSTAR Research Inc. Pvt. Ltd.,
Ahmedabad, Gujrat, India

²Global Institute of Stem Cell Therapy
and Research, 4660 La Jolla Village
Drive, San Diego, CA 92122, USA

*Author for correspondence:
Email: anand@giostar.com

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Abstract

Scalp psoriasis, a skin condition characterized by red, thickened (erythematous), well-demarcated patches or plaques with overlying silvery-white scales, affecting part or all of the scalp, is an autoimmune disease accompanied by itchy skin. The disease is associated with faulty functioning of adaptive and innate components of immune systems. The key pro-inflammatory cytokines mediating immunopathology of psoriasis are IL-17 and IL-23 which promote proliferation of Th 17 cells which in turn induce proliferation of keratinocytes leading to the disease. Standard management of psoriasis primarily targets the disease by suppression of inflammation using steroid based drugs. However, these are not enough to cure the disease. In recent years researchers have demonstrated the use of mesenchymal stem cells (MSCs) in treating autoimmune disorders and skin disorders. MSCs mediate skin regeneration by a plethora of mechanisms including immune modulation, angiogenesis, proliferation of mediator cells like fibroblasts, and by inhibition of pro-inflammatory pathways. The paracrine factors secreted by MSCs, in surrounding environment, like growth factors, cytokines, chemokines, and other signaling and regulatory molecules, act as key molecules in mediating anti-inflammatory responses. Here, we describe a case report following the treatment of a patient suffering from scalp psoriasis using MSC- secreted molecules in the conditioned media. Both silvery scales and plaques on the scalp were significantly reduced within 4 weeks of topical application of the conditioned media. The patient remained disease free for 3 years of follow up. Our current results are in good agreement with those of our previous report where we reported complete amelioration of scalp psoriasis following the topical application of the conditioned media.

Introduction

Psoriasis, a fairly common disease affecting about 2-3% of people worldwide, affects people of all age groups irrespective of their ethnicity. It is a disease rooted in inflammation leading to issues regarding skin, nails, and joints. Psoriasis is marked by symptoms such as erythema, scaling, itching, inflammation, and the feeling of burning. The most common form of the disease is plaque psoriasis characterized by the presence of well demarcated erythematous plaques with scaly skin. The color of the scales ranges from silvery white to orange-brown. The disease has been found to be associated with arthritis known as psoriatic arthritis. Further, associations with obesity and metabolic syndromes have also been reported. In some cases, quality of life is impaired as the symptoms affect not only physical appearance but also impact the patients at psychological level causing low self-esteem in them. Overall, the quality of life is compromised in psoriatic patients [1].

Advances in the field of pathophysiology of psoriasis have unveiled roles of misguided immune system and underlying genetic components leading to it. The crosstalk between innate and adaptive components of the immune system has been suspected to be responsible for playing key roles in etiology of psoriasis. The central molecules involved in this signaling network are IL-23 and IL-17. IL-17 is produced by specific T cells termed as Th17 cells. Upon activation by signal molecules, like those present in streptococcal extracts, the number of Th17 cells increases. Activated Th17 cells secrete different cytokines causing proliferation of keratinocytes. These activated keratinocytes stimulate more IL-17 secretion leading to formation of positive feedback loop. This cycle results in inflammation in the skin [2].

The genome-wide association studies (GWAS) have indicated the role of single nucleotide polymorphism (SNPs) in the genes that encode factors for antigen presentation, responsible for psoriasis. Human leucocyte antigen (HLA) class I genotypes (HLA-C*06 and HA-B*57) are such genes associated with skin psoriasis. HLAs bind to autoantigens and get antigens recognized by the immune system leading to immune activation. Autoantigens like antimicrobial peptide LL37 and melanocyte autoantigen ADAMTSL5 bind to HLA-C*06:02 and activate CD4+ and CD8+ T cells. The genome studies also have suggested the involvement of psoriasis associated genes in encoding of several cytokines and receptors which are responsible for causing disease. The gene loci of IL12B and IL23R encode heterodimeric protein IL-23, the key mediator of pathogenesis [2].

The above investigations have helped in unravelling the molecular and immunological pathways involved in etiology of the disease. However, currently medical interventions do not provide sufficient help in curing the disease, and therefore, it is still only managed at clinical level. This fact demands the exploration of novel molecules, of chemical or biological origin, which can modulate the key underlying pathways leading to psoriasis in order to cure it.

Mesenchymal stem cells (MSCs) are multipotent adult stem cells found in several organs including bone marrow, adipose tissue, liver, gut, dental pulp, umbilical cord, placenta etc. MSCs are characterized by spindle shaped fibroblast-like structures marked by presence of CD 73, CD90, CD105 and absence of CD3, CD14, CD34, and CD45 markers. These cells under specific culture conditions *in vitro* can stay undifferentiated and can proliferate for periods depending on their source of origin. MSCs can differentiate into cells of osteogenic, chondrogenic and adipogenic lineages depending on the cell signaling they come across. The MSCs exert therapeutic effects through several mechanisms resulting in anti-inflammation,

immunomodulation, anti-oxidation, anti-apoptosis, anti-fibrosis, and angiogenesis. MSCs mediate these key activities through secretion of several cell signaling molecules in the surrounding environment. The MSCs secretome consists of a number of cell signaling molecules like growth factors, cytokines, chemokines, metallo-proteinases, exosomes, small RNA etc. These molecules secreted by the MSCs can help reverse the imbalance created in innate and adaptive immunity. MSCs also can inhibit proliferation of the dendritic cells, T and B cells as well as can inhibit expression of DC surface markers like CD80, CD83, CD86 leading to inhibited antigen presentation process. Besides, MSCs can also downregulate the pro-inflammatory Th17 cells. The immunomodulatory activity of MSCs is associated with secretion of interleukin 10 (IL-10), transforming growth factor- β (TGF- β), nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), and prostaglandin E2 (PGE2) [3].

Studies have reported impaired MSC functions in those derived from psoriatic plaques. These MSCs have decreased differentiation potential and immunoregulatory capabilities. Furthermore, such aberrant MSCs promote keratinocyte proliferation leading to thickening of the epidermis [4-5].

In the case discussed below, we report the complete disappearance of silvery scales and plaques due to psoriasis in a patient following the topical application of MSC secretome present in conditioned media in a very short duration of four weeks only.

Case Report

A 32-year-old male suffering from scalp psoriasis for about 3 years approached to our clinic in Ahmedabad. The patient had silvery scaly skin on the back of the scalp and behind the ears (**Figure 1**). Numerous plaques were visible in and around the scaly areas. The skin was dry, and the patient had severe itching in the affected areas. The patient had received steroid based ointments and drug treatments



Figure 1. Image demonstrating scalp psoriasis with silvery scales and plaques.

but was not getting cured. Due to lack of sufficient curative response following the conventional therapeutic interventions, the patient was willing to try other available clinical interventions. Based on results of previous reports including that from our clinic, MSC-derived conditioned media was prescribed to the patient for topical application on the affected areas. The patient was informed about the nature of intervention in advance and prior informed written consent was obtained in advance.

MSCs, used for the preparation of the conditioned media, were isolated from adipose tissue, and MSC-conditioned media was collected as described previously. Briefly, the adipose tissue, collected from a healthy willing donor by a plastic surgeon under aseptic conditions, was immediately transferred to our laboratory for further processing. MSCs were isolated and cultured for 3 weeks. The conditioned media was collected and then concentrated 10 times using 3 KDa ultrafiltration membranes. The concentrated media was stored at -20°C until further use. The patient applied 1-2 ml of MSC-conditioned media topically on the affected areas only once a day for a period of 4 weeks. The progress was evaluated in terms of severity of psoriatic plaques and approximate number of silvery scales on a weekly basis up to 6 months.

During the follow-ups, no adverse events were reported by the patient. During the examination of disease affected areas it was detected that silvery scales and plaques were reduced. Following the 4 weeks of application, we observed a significant reduction in psoriatic plaques, elimination of silvery scales altogether, and restoration of skin color to normal (**Figure 2**). During the course of treatment and follow-ups, the patient did not receive any other medication for the disease. The patient has been free of related symptoms for three years and has improved quality of life.

Discussion

Roles of MSCs in wound healing in general and in skin related ailments have been investigated by researchers. Studies have demonstrated that *in vivo* infusion of MSCs can exert therapeutic effects in animal models as well as in humans. These effects have been attributed to molecules secreted by MSCs, modulating the host immune environment leading to skin regeneration.

Preclinical studies using imiquimod (IMQ) induced psoriasis have demonstrated the MSC-mediated inhibition of T cells and dendritic cells (DCs) leading to significant reduction in severity of psoriasis. A number of studies using intradermal injection of adipose derived MSCs showed reduction in IMQ induced skin inflammation [6-9]. Reduced pro-inflammatory cytokine production by aberrant MSCs derived from psoriasis plaques was seen when cocultured with dermal MSCs derived from healthy control [10]. In a report by Wang et al, a complete remission was observed in a patient with 5 year of plaque psoriasis history following the allogeneic gingival MSC infusion. The patient stayed disease free for 3 years of the follow up [11]. Similarly, another study reported a reduction in PASI score from 9.9 to 1.7 after transplantation of minimally manipulated umbilical cord derived MSCs in a psoriatic patient [12].

In this case, we report a complete reversal of the symptoms caused due to skin psoriasis in a patient. The patient with typical symptoms of skin psoriasis was offered to apply MSC-conditioned media. Topical application of the conditioned media resulted in clearing of the silvery scales and elimination of plaques on the scalp region within 4 weeks of the application. The skin color was restored to normal, and the patient realized a better quality of life. These observations are in good agreement with our previous report where we observed a complete remission of scalp psoriasis in a patient



Figure 2. Post treatment images of scalp psoriasis below the occipital region in neck of patient. Reduction of silvery scales and plaques in scalp psoriasis post treatment follow up at 2 weeks (a) and 4 weeks (b).

with erythematous plaques and silvery scales after similar treatment. These anti-psoriatic effects and skin regeneration could be attributed to paracrine cell-signaling pathway modifying molecules present in the conditioned media. Anti-inflammatory cytokines including IL-10 and IL-4 present in conditioned media could be responsible for inhibiting inflammation. This is further supported by the evidence that MSCs derived from psoriatic skin lack the normal profile of secreted cytokines due to presence of circular RNAs and thus fail to inhibit lymphocyte proliferation [13,14]. Further, MSCs also secrete antimicrobial peptide LL37 which helps in antimicrobial activities. The MSC secretome contains a number of molecules like basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), keratinocyte Growth Factor (KGF), and TGF- β which trigger processes of tissue repair. These molecules stimulate the proliferation of epidermal cells, fibroblasts, endothelial cells, and help in cell migration and cell survival by affecting gene expression of key regulatory genes. Further, molecules in the MSCs secretome also act as chemoattractant for dermal fibroblasts, macrophages, epidermal keratinocytes and help in recruitment of those cells in the healing processes including closure of the wound. VEGF and HGF molecules help in exerting anti-scar activities [15].

Conclusion

Here, we report another case of scalp psoriasis, where the patient realized the therapeutic benefits of MSCs derived conditioned media. In general, the conditioned media derived from MSCs culture contains a number of secreted cell signaling molecules. Topical application of the conditioned media resulted in reduction of silvery scales, psoriatic plaques, and restoration of affected skin to the normal. Our report opens a new direction towards the possibility of using MSCs secretomes in cases of psoriasis patients. This report further underscores the benefits of using cell free biomolecules which reduces the risk associated with stem cell transplant while providing full therapeutic benefits of stem cells even when used topically.

Consents

The patient consented to participate in this study and for the findings published. The volunteer willingly donated the visceral fat used for preparing the MSCs.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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