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The First Live-Cell Based Product in The Iranian Drug List; ReColorCell®

Mohammad Amin Shahrbaf, M.D., Leila Ataei Fashtami, M.D., Massoud Vosough, M.D., Ph.D.*

Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran

Abstract

Vitiligo is an autoimmune skin disorder that can significantly affect the quality of life in patients. However, current treatment strategies such as phototherapy, topical glucocorticosteroids, or systemic immunosuppressants can be helpful in vitiligo management, and treatments for disease stability which is the main challenge in vitiligo management. Novel therapeutic modalities have made promising advances in this regard. Molecular targeted therapy to target Janus-activated kinase (JAK) such as Tofacitinib and Ruxolitinib in addition to the cell-based treatments are innovative therapeutic options, which are recently used for vitiligo treatment. Transplantation of non-cultured melanocytes-keratinocytes have been studied in Iran and phase one data published in 2010 on 10 patients that continued on 300 patients as phase three in 2018. Cell Tech Pharmed™ Co. registered and applied this cell-based product, ReColorCell®, as a GMP certified by Iranian Food and Drug Administration (IR-FDA). On 11th December 2021, ReColorCell® officially registered as the first cell-based product in the Iranian drug list (IDL). Currently, the post-market study of this product is ongoing.

Keywords: Cell Therapy, Keratinocyte, Melanocyte, Vitiligo

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Vitiligo is a complex autoimmune skin disorder manifest by hypo- or depigmentation of affected skin due to the destruction of the functional melanocytes by cytotoxic T cells (1). This disease has a multifactorial nature, in which, mainly genetic predisposition and environmental triggers can elucidate the immune response against melanocytes (2). Vitiligo has a global prevalence of 0.5-2% (3); however, it can significantly affect the self-confidence of the patients due to its aesthetic outcomes and dramatically decrease the quality of life in the patients (4). Several clinical setting proposed for treating vitiligo patients including phototherapy, topical agents such as gluco-corticosteroids, calcineurin inhibitors, or systemic immunosuppressants (5); The main challenging issue in treating vitiligo is relapse prevention and pigmentation maintenance after successful treatment. Usually relapse occurs in 40% of the patients (6). In a study in 2020, it was revealed that almost 50% of vitiligo patients were not satisfied with current treatment modalities and almost 95% of them were believed novel therapeutic options are necessary (7). The main pathophysiology for relapses related to memory T-cells of the skin and effective inhibition of these immune cells can cause maintenance in treatment (8). During recent years, innovative therapeutic options such as molecular targeted therapy and cell-based treatments have made prominent progress in the treatment of chronic disorders such as vitiligo (9, 10). Targeting Janus-activated kinase (JAK) medications such as Tofacitinib, Ruxolitinib, Baricitinib, Ifidancitinib, Ritlecitinib, and Cerdulatinib or targeting Wnt signaling pathway by specific ligands are some examples of molecular targeted therapy (11). Administrating cell-based products such as autologous melanocytes for treating vitiligo have been associated with promising results in recent decades (12). In addition, given the immunomodulatory properties of mesenchymal stromal cells (MSCs), cell-based therapies could be a potential targeted therapy for vitiligo patients (13).

It was shown that MSCs can ameliorate the underlying pathology of vitiligo through regulating phosphatase, tensin homolog (PTEN) expression and improving melanocyte proliferation in experimental models (14). Transplantation of cultured melanocytes or non-cultured melanocytes–keratinocytes have been used for cell-based therapies in clinical settings (15). Autologous cell-based products were firstly used by Guerra et al. (16) in a clinical trial in 2003 and associated with significant repigmentation rate in stable lesions. In Iran, cell-based therapy for vitiligo was firstly conducted at Royan institute through

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***Corresponding Address: P.O.Box: 16635-148, Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran**
Email: masvos@royaninstitute.org

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intraepidermal transplantation of autologous epidermal cells in suspension for 10 vitiligo patients in 2010. This study associated with no side effects and significant repigmentation in 40% of patients with mild to moderate repigmentation in the other patients (17). The second study in Royan institute that assessed the long-term efficacy of autologous epidermal cells transplantation in 300 patients with stable vitiligo published in 2018, associated with effective repigmentation (more than 50%) in almost 30% of the patients in the majority of treated patches over the 36 months follow-up (18). These two clinical trials suggested the safety and efficacy of this innovative cell-based approach and this product called ReColorCell®.

Stem cell science and regenerative medicine have gain momentum in recent two decades in Iran (19). Considering that national drug development plans should be under registration of local food and drug administration (20), the production and market authorization of any cell-based product should be conducted under the consideration of Iranian Food and Drug Administration (IR-FDA). Cell Tech Pharmed™ Co., an Iranian stem cell and regenerative medicine company, is one of the best cell-manufacturing companies in the Middle East, which was established on 19th February 2014. This facility is GMP certified for four products, manufacture and distribute stem cell platform technologies based on tech-development programs at the Royan Institute and Barakat Pharmaceutical Group. This company is a pioneer facility for advanced medicinal therapeutic products (ATMPs) for clinical application in the region. Four different cell products, including RenuDermCell® (autologous dermal fibroblast), MesestroCell® (autologous bone marrow derived MSCs), ReColorCell® (autologous melanocyte-keratinocyte), and WhartoCell® (allogenic umbilical cord derived Wharton's jelly MSCs) have been authorized by IR-FDA and good manufactured practice (GMP) certified in 2018 (for first three products) and 2020 (for WhartoCell®) so far.

In 6th February 2018, Cell Tech Pharmed™ Co. applied ReColorCell® as a novel cellular/gene-based therapeutic product to be registered in the Iranian drug list (IDL). Production line and process of this live cell-based product was already GMP-certified by IR-FDA at Cell Tech Pharmed™ Co. After further investigation by IR-FDA, based on the safety and efficacy profiles published in the mentioned clinical trials (17, 18) and checking all documents, IR-FDA decided to invite Celltech Pharmed ™ representative to IDL committee on 3rd October 2021. This committee is a national supreme board of summits composed of scientists, clinicians, and regulatory affairs specialists. After the 513th official meeting of IDL committee at IR-FDA at 11th December 2021, ReColorCell® officially registered as the first cell-based product in IDL for clinical application. ReColorCell® was registered at IR-FDA under "Biological Products Bureau" and all documents related to clinical studies were monitored by "Clinical Studies Bureau" at IR-FDA. After five years of intensive audit, continuous investigation and monitoring all the documents, IR-FDA approved termination of phase III on 11th December 2021. Cell Tech™ Pharmed Co. should continue post market study and update regularly authorities at "Clinical Studies Bureau" under IR-FDA. The post market study started recently. Comparison of ReColorCell® with other existing treatments in terms of possible lower relapsing rate, cost-effectiveness, and feasibility for treatment will be available based on post market data.

We hope in the future, more knowledge-based products get market authorization in Iran and help patients suffering from complicated disorders.

Cell-based therapies can represent as cellular immunotherapies, cancer vaccines, and autologous/allogeneic cells for therapeutical application in order to repair or replace damaged tissues. Based on the office of tissues and advanced therapies (OTAT) of FDA, 27 cellular/gene-based therapeutic product are approved until the end of 2022 (https://www.fda.gov/approved-cellular-and-gene-therapy-products). It means that the number of approved ATMPs is growing rapidly. Entering ReColorCell® in the IDL opened a shining way for ATMPs in the country and provided the opportunity for other knowledge-based companies to register more products and apply for market authorization.

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Authors' Contributions

M.V., L.A.F.; Contributed to conception and design. M.A.S.; Drafted the manuscript, which was revised by M.V. All authors read and approved the final manuscrip

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