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Application of the cultured epidermal autograft "JACE®" for treatment of severe burns: Results of a 6-year multicenter surveillance in Japan

Hajime Matsumura [a,*], *Asako Matsushima* [b], *Masashi Ueyama* [c], *Norio Kumagai* [d]

[a] *Department of Plastic and Reconstructive Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan*

[b] *Department of Advancing Acute Medicine, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi Aza Mizuhocho Mizuho-ku, Nagoya 467-8602, Japan*

[c] *Department of Trauma, Critical Care Medicine and Burn Center, Japan Community Healthcare Organization Chukyo Hospital, 1-1-10 Sanjo, Minami-Ku, Nagoya 457-8510, Japan*

[d] *St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-Ku, Kawasaki, Kanagawa, 216-8511, Japan*

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ABSTRACT

Background: In the 1970s, Green et al. developed a method that involved culturing keratinocyte sheets and used for treatment of burns. Since then, the take rate of cultured epidermal autograft (CEA) onto fascia, granulation tissue, or allografts has been extensively reported, while that on an artificial dermis in a large case series is not. Moreover, the contribution of CEA to patient survival has not been analyzed in a multicenter study.

Methods: We conducted a 6-year multicenter surveillance on the application of the CEA "JACE®" for treatment of burns >30% total body surface area (TBSA) across 118 Japanese hospitals. This surveillance included 216 patients and 718 graft sites for efficacy analysis. The CEA take rate at 4 weeks after grafting was evaluated, and safety was monitored until 52 weeks. In addition, the survival curve obtained in this study and the data obtained from the Tokyo Burn Unit Association (TBUA) were compared.

Results: The mean CEA take rates at week 4 were 66% (sites) and 68% (patients), and the rate on the artificial dermis was 65% for 226 sites. CEA application combined with wide split-thickness auto or patch autograft increased the CEA take rate. On comparison with the data obtained from the TBUA, which included data on individuals with burns of the same severity, CEA application was found to contribute to patient survival until 7 weeks after burn.

Conclusions: We reported the take rate of CEA based on a 6-year multicenter surveillance. From our results, we found that the application of CEA is a useful treatment for the patients with extensive burns.

* *Corresponding author*. Tel.: +81 3 3342 6111; fax: +81 3 5322 8253.
E-mail addresses: hmatsu-tki@umin.ac.jp (H. Matsumura), asakouab@gmail.com (A. Matsushima), m.ueyama@gmail.com (M. Ueyama), kumano952@gmail.com (N. Kumagai).

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1. Introduction

Loss of skin over a wide area severely impairs its vital functions, which include maintaining the body temperature, conserving fluids, and resisting infection by bacteria that invade the body from the external environment; it also increases the risk of death. Keratinocytes that comprise the epidermis possess an extremely high proliferative ability, thus causing rapid regeneration of skin.

In the 1970s, Green et al. cultured keratinocytes along with mouse-derived 3T3 cells to form keratinocyte sheets; this method is currently known as Green's technique for culturing epidermis [1,2]. Based on this pioneering research, a cultured epidermis that could be grafted onto the injured area was developed by isolating keratinocytes from a skin biopsy and culturing them in flasks, which then form a skin-like sheet [3,4].

When a cultured epidermis grown from the patient's own cells is grafted, it does not elicit immune rejection and is instead incorporated into the patient's own skin. The cultured epidermis was originally used to save the lives of patients with severe burns [5].

In 1984, this technique attracted worldwide attention when two children with severe burns survived. The technique enabled the generation of 5000–7000 cm^2 of cultured epithelium for grafting, prepared from the limited remaining skin of the children following burn [6]. Cultured epidermis prepared by Green's technique has invariably played a major role in advancing the development of regenerative medicine in many countries [7].

The first commercially available cultured epidermal autograft (CEA) product used for the treatment of extensive burns was "Epicel®," which was launched in the late 1980s [8]. The CEA "JACE®" was also prepared using Green's technique, approved, and then used for the treatment of victims with burns over 30% TBSA (total body surface area) in Japan from 2007 onward; it was also covered by public health-care insurance.

Although Sood et al. reported the high take rate of CEA and its usefulness in the treatment of extensive burns, no large-scale, multi-institutional data have been published. Moreover, CEA has not gained prominence in the treatment of extensive burns in the United States [9].

To date, the CEA take rate has been reported only on the fascia and granulation tissue after allografting in the case series. As there are no reports about the efficacy or take rate on the artificial dermis, which is used for dermal regeneration before CEA use [10,11], the take rate in various grafting conditions must be determined. Moreover, no statistical data confirming the role of CEA in the survival of victims with burns are available except for Kym's data, which were obtained by a single institutional nonrandomized study [12].

The Japanese Ministry of Health, Labor and Welfare and the Pharmaceuticals and Medical Devices Agency requested the surveillance of all patients with severe burns who were treated with JACE® across every institution in Japan. Therefore, in this manuscript, we report the results of this surveillance. In addition, to determine whether CEA contributed to patient survival, we compared the survival curve plotted with the data obtained in this study with the data from the Tokyo Burn Unit Association (TBUA), which included data on victims with burns of the same severity.

2. Methods

2.1. Ethical considerations

JACE® consists of sheets of autologous cultured keratinocytes produced using Green's technique. It is indicated for use in patients with severe, extensive burns; the total area of deep second-degree (deep dermal) and third-degree (full-thickness) burns is ≥30% of the TBSA. The post-marketing all-case surveillance of JACE® was requested by the Japanese Health, Labor, and Welfare Ministry as a condition for the product's approval. The survey protocol was accepted by the regulatory authorities and was approved by the institutional review board of each hospital, and surveillance was performed under the contract, which was agreed upon by all the hospitals.

2.2. Surveillance design and patient enrollment

The principal objectives were to assess the effectiveness and safety of the CEA. The former was assessed using the take rate (i.e., the percentage of epithelialization) in the grafted area of the burn wound, and the latter was assessed using the incidence of serious adverse events such as tumorous conditions, allergic reactions, or critical infections.

The take rate of CEA can be confirmed within the first 4 weeks; hence, the effectiveness was assessed by the reepithelialization rate at week 4 following application of CEA. The assessments for effectiveness and safety (i.e., graft site observation and whole body safety) were performed until week 52 after applying CEA. The consort flow diagram for this study is shown in Fig. 1.

The surveillance period for each patient was divided according to the day of placement of CEA: the pretreatment and treatment periods. Between October 2007 and October 2014, 515 patients had started undergoing the CEA treatment procedures, and they were enrolled during the collection of skin biopsies. The safety population for the pretreatment period included 414 patients whose case report forms were recovered from 118 Japanese hospitals or departments with consent for this analysis; patients who were already under surveillance were excluded. The safety population during the treatment period included 280 patients who were numerically matched to those who underwent treatment with CEA. The CEA was prepared by cultivating keratinocytes, which were isolated from patients' own skin tissue for ≥3 weeks.

The reasons for discontinuing CEA in 134 cases included death during the preparation of CEA by cultivating keratinocytes for ≥3 weeks after biopsy ($n = 108$), recovery during the preparation of CEA and hence no use of CEA ($n = 17$), other causes ($n = 7$), adverse events ($n = 1$), and loss to follow-up ($n = 1$). The efficacy population included 260 patients; 19 rapid deaths and one patient who changed hospitals without undergoing an evaluation after CEA were excluded. The week 4 efficacy analysis included 216 patients who underwent evaluation for epithelialization at week 4.