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COMMENTARY

Autologous Skin Cell Suspension for Full-Thickness Skin Defect Reconstruction: Current Evidence and Health Economic Expectations

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ABSTRACT

Despite differing etiologies, acute thermal burn injuries and full-thickness (FT) skin defects are associated with similar therapeutic challenges. When not amenable to primary or secondary closure, the conventional standard of care (SoC) treatment for these wound types is split-thickness skin grafting (STSG). This invasive procedure requires adequate availability of donor skin and is associated with donor site morbidity, high healthcare resource use (HCRU), and costs related to prolonged hospitalization. As such, treatment options that can facilitate effective healing and donor skin sparing have been highly anticipated. The RECELL® Autologous Cell Harvesting Device facilitates preparation of an autologous skin cell suspension (ASCS) for the treatment of acute thermal burns and FT skin defects. In initial clinical trials, the approach showed superior donor skin-sparing benefits and comparable wound healing to SoC STSG among patients with acute thermal burn injuries. These findings led to approval of RECELL for this indication by the US Food and Drug Administration (FDA) in 2018. Subsequent clinical evaluation in non-thermal FT skin wounds showed that RECELL, when used in combination with widely meshed STSG, provides donor skin-sparing advantages and comparable healing outcomes compared with SoC STSG. As a result, the device received FDA approval in June of 2023 for treatment of FT skin defects caused by traumatic avulsion or surgical excision or resection. Given that health economic advantages have been demonstrated for RECELL ± STSG versus STSG alone when used for burn therapy, it is prudent to examine similarities in the burn and FT skin defect treatment pathways to forecast the potential health economic advantages for RECELL when used in FT skin defects. This article discusses the parallels between the two indications, the clinical outcomes reported for RECELL, and the HCRU and cost benefits that may be anticipated with use of the device for non-thermal FT skin defects.

Keywords: Autologous skin cell suspension; Split-thickness skin graft; Thermal burn injury; Full-thickness skin defect; Trauma surgery; Soft

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tissue reconstruction; Length of stay; Cost savings; Health economics

Key Summary Points

Although etiologies differ, acute thermal burn injuries and full-thickness (FT) skin defects have similar clinical features and challenges related to patient burden and management.
The conventional standard of care for both wound types, split-thickness skin grafting (STSG), is associated with donor site morbidity and elevated healthcare resource use (HCRU) and costs.
In clinical trials of acute thermal burn injuries and FT skin defects, treatment with autologous skin cell suspension (ASCS) ± STSG was associated with superior donor skin-sparing benefits and comparable wound healing versus STSG alone.
Health economic analyses show that use of ASCS ± STSG in acute thermal burn injuries results in reduced length of stay in hospital, fewer autograft procedures, lower rehabilitation costs, and reduced overall costs compared with use of STSG.
Given the numerous parallels in the characteristics and management of acute thermal burn injuries and FT skin defects, as well as positive clinical outcomes with ASCS, it is reasonable to expect that similar HCRU and cost benefits may be expected with use of ASCS in FT skin defect reconstruction.

INTRODUCTION

The RECELL® Autologous Cell Harvesting Device (RECELL System; AVITA Medical, Valencia, CA) is a donor skin-sparing approach used to prepare a regenerative autologous skin cell suspension (ASCS) that supports restoration of skin wounds. Used worldwide for a variety of therapeutic indications, the device was first approved by the US Food and Drug Administration (FDA) in 2018 for the treatment of acute thermal burn injuries [1]. In June 2023, the FDA granted clearance of the pre-market approval (PMA) supplement for use of RECELL in combination with split-thickness skin grafting (STSG) for full-thickness (FT) skin defects arising from traumatic avulsion or surgical wounds, such as those related to necrotizing soft tissue infection or cancer [1]. Also in June of 2023, the FDA granted PMA clearance for use of RECELL for the repigmentation of stable depigmented vitiligo lesions [2].

As detailed in this commentary, closure of FT thermal and non-thermal skin wounds is similar in terms of often requiring autografting to transplant healthy skin to close the wound site. Although effective, use of STSG can lead to considerable donor site pain, invasive wound care needs, and prolonged length of stay (LOS) in hospital [3–11]. In clinical trials of patients with FT burns and non-thermal FT defects, use of RECELL-prepared ASCS in combination with widely meshed STSG was associated with superior autograft-sparing and comparable skin healing to conventional autografting [12, 13]. In the acute burn setting, these effects have translated into clear health economic advantages over use of STSG alone [11, 14–16]. As such, it is of high interest to examine whether the clinical benefits of RECELL-prepared ASCS observed in non-thermal FT defects may similarly translate into economic value.

This article examines commonalities in the therapeutic goals, needs, and challenges associated with management of FT burns and non-thermal skin defects, summarizes the clinical outcomes observed to date with ASCS when used for these indications, and discusses the healthcare resource use (HCRU) and cost benefits that may be realized with use of RECELL in the new FT defect setting. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

TREATMENT OF ACUTE BURN INJURIES AND NON-THERMAL SKIN DEFECTS: CHALLENGES AND UNMET NEEDS

Acute thermal burn injuries result from application of direct heat to the skin via an open source such as fire, steam, or contact with hot objects or liquids [17]. Such insults can lead to destruction of the skin, which may result in loss of skin functionality and homeostasis and even patient death [18]. Although these injuries occur most frequently within the home [19], they may also result from mass casualty disasters such as industrial accidents [20, 21]. Non-thermal FT skin defects represent another type of skin wound. Arising from high-energy traumatic insults or surgical excision or resection, these injuries vary in characteristics and may originate from degloving and crush injuries, skin lacerations, gunshot or surgical wounds, necrotizing infections, or skin cancer treatment.

Despite differing etiologies, FT thermal burn injuries and FT skin defects are similarly associated with a high clinical and economic burden [22–27]. In the USA, these wound types impact tens of thousands of patients each year [19, 28] and are associated with substantial pain, infection, scarring, reduced functionality and quality of life (QoL), and an elevated risk of mortality [23, 24]. Patients with these injuries are frequently concerned about aesthetic appearance and the ability to return to normal activities including work [23], as prolonged inpatient treatment is sometimes required for healing [17]. Collectively, these factors contribute to a considerable economic impact that arises directly from wound treatment and hospitalization costs and indirectly in the form of lost work productivity and lost years of life [22, 25–27]. In the USA, the economic burden (including medical costs, work costs, and QoL costs) of non-fatal injuries is extensive, costing an estimated $2 trillion in 2019, with non-fatal burn injury hospitalizations and emergency room visits alone totaling more than $11.5 billion [27, 29].

Although not identical, acute FT burns and non-thermal FT skin defects also share commonalities related to the deleterious effects of conventional wound closure strategies. In both settings, the goal of therapy is rapid and durable wound healing with minimization of patient morbidity. For wounds unamenable to primary or secondary closure techniques, the historical standard of care (SoC)—STSG—is an invasive procedure that requires adequate availability of donor skin for transplantation, as surgeons must create a commensurately sized wound to treat the primary injury. Creation of such donor skin wounds can be troublesome for patients, being associated with significant pain and risk of infection, scarring, discoloration, and psychological issues [3–10]. Additionally, concerns arise for patients who have large donor skin requirements yet limited availability of useable donor skin. This is especially the circumstance for individuals with high total body surface area (TBSA) wounds or pediatric and elderly populations with thin, fragile tissue [30, 31]. For these patients, lack of donor skin can be mitigated by use of mechanical devices that mesh the skin, thereby helping to expand the coverage area; however, large expansion ratios are typically avoided by surgeons because of extended healing and scarring concerns. Another option is the performance of a series of skin harvesting procedures [23], but these require prolonged LOS in hospital and have increased treatment burden and costs [3, 11, 15, 32]. A such, minimization of donor skin requirements is critical to address these physical, emotional, and resource use issues and is imperative for patients with limited usable skin and/or who are prone to delayed healing (e.g., because of comorbidities) [30, 31, 33–36]. Treatment approaches that support definitive wound closure while reducing donor skin harvesting and without comprising patient safety or scarring outcomes have therefore been highly anticipated in both acute thermal and non-thermal wound care settings.

THE RECELL AUTOLOGOUS CELL HARVESTING DEVICE

The RECELL System is a single-use, stand-alone, point-of-care device that includes enzymatic

and delivery solutions, sterile surgical instruments, and actuators [1]. This skin grafting approach enables enzymatic and mechanical processing of a small, thin split-thickness skin sample into an ASCS that includes disaggregated keratinocytes, fibroblasts, and melanocytes [37]. These cell types are essential for wound re-epithelialization (healing) and pigment restoration [38, 39]. In the treatment of FT skin injuries, each square centimeter of donor skin sample can be used to prepare 1 mL of cell suspension for treatment of up to 80 cm^2 of wound area [1]; a single RECELL device can treat wound areas up to 1920 cm^2 in size. The prepared ASCS, used in combination with widely meshed STSG for FT skin wounds, is applied to a clean, vascularized wound bed using a spray technique. This treatment approach promotes epidermal regeneration for definitive wound closure while minimizing donor skin requirements and their associated burden.

In the USA, the RECELL System is currently approved by the FDA for the treatment of thermal burn wounds and FT skin defects, as well as repigmentation of stable depigmented vitiligo [1, 2]. The device is also registered with the Therapeutic Goods Administration in Australia [40], maintains CE Mark approval in Europe, and has approval from the Pharmaceuticals and Medical Devices Agency in Japan [41] for various skin-related indications. Notably, the RECELL System was granted US FDA Breakthrough Designation for all three approved indications [42]. This designation supports timely patient access to medical devices that offer effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions [43].

CLINICAL BENEFITS OF ASCS IN ACUTE THERMAL BURN WOUNDS

Key evidence for the safety and effectiveness of ASCS ± STSG in burn treatment is available from two prospective, randomized, phase III clinical trials, which were partially funded by the Biomedical Advanced Research and Development Authority (BARDA) in an effort to increase burn care preparedness [1, 12, 44]. Additional data are available from retrospective analyses of patients enrolled in expanded and continued access protocols, including pediatric patients and those with greater than 50% TBSA FT wounds [1].

In one of the phase III trials, ASCS + STSG was compared with SoC STSG alone among patients with mixed-depth thermal burns, including FT injuries [12]. The study population included 30 patients aged 5 years or older presenting with 5–50% TBSA burn wounds requiring autografting for closure. A within-patient control design was employed, in which treatment areas were randomly assigned to control (STSG alone, meshed according to the surgeon's SoC) or ASCS + more widely meshed (one ratio higher) STSG treatment. The study results were favorable for both co-primary endpoints, which included non-inferiority of ASCS + STSG to STSG alone for complete treatment area closure (100% re-epithelization) at or before week 8 and superiority for relative reduction in donor skin requirements. Non-inferiority of ASCS + STSG was established for wound healing at week 8, with 92.3% versus 84.6% of STSG-treated patients showing complete closure (treatment difference, − 7.7% [one-sided 97.5% CI upper bound, 6.40%]). Additionally, superiority of ASCS + STSG was established for relative reduction of donor site harvesting: on average, 32% less donor skin was required with ASCS + STSG than STSG alone ($p < 0.001$). Secondary endpoints, including patient satisfaction, Patient and Observer Scar Assessment Scale (POSAS) scores, and safety profiles were comparable between treatment areas.

In the other phase III trial of ASCS, which focused on deep partial thickness (DPT) burns, ASCS treatment alone was also associated with comparable healing and significantly greater donor skin sparing than 2:1 meshed STSG [44]. Additionally, greater overall patient satisfaction, faster healing, and reduced pain and scarring were reported for ASCS donor sites compared with STSG donor sites [44]. In both phase III studies, the benefits of ASCS were observed without compromising patient safety.

CLINICAL BENEFITS OF ASCS IN FT SKIN DEFECTS

The pivotal trial for use of ASCS in FT skin defects was a prospective, multicenter, randomized, controlled, evaluator-blinded study (NCT04091672) [13]. The study population included 65 patients aged 5 years and older presenting with a FT defect ($\geq 160\ cm^2$, $\leq 50\%$ TBSA) requiring autografting. The trial had a within-patient control design, with random assignment of study areas to control (STSG alone, meshed according to the surgeon's SoC) or ASCS + STSG meshed one ratio higher. Similar to the study of FT burns, primary and co-primary effectiveness endpoints included non-inferiority of ASCS + STSG to STSG for complete closure (100% re-epithelialization) at week 8 and superiority of ASCS + STSG over STSG for relative reduction in donor skin area requirements. Safety outcomes focused on treatment-emergent adverse events (TEAEs) of interest, including delayed healing, infection, and wound durability. ASCS + STSG was shown to be non-inferior to STSG alone for complete closure at week 8 (65% vs. 58%; $p = 0.005$) [13]. Furthermore, ASCS + STSG was associated with a significant donor skin-sparing effect: on average, 27% less donor skin was required compared with use of STSG alone, establishing superiority of ASCS + STSG. The treatment approaches had comparable efficacy for clinical healing ($\geq 95\%$ re-epithelization) and long-term scarring results (POSAS scores). Safety profiles were also comparable, with a similar frequency of TEAEs of interest observed between treatment areas. In case reports and case series of patients presenting with various non-thermal tissue defect types, ASCS has also shown favorable outcomes related to healing, donor site size, and aesthetic appearance [45–50].

ECONOMIC VALUE OF ASCS IN THERMAL BURN INJURIES

In light of the positive clinical findings for RECELL in thermal burn treatment and the substantial financial burden associated with burn management in the USA, modeling and real-world data (RWD; i.e., data from daily clinical practice) analyses have been conducted to evaluate the health economic implications of introducing ASCS ± STSG [11, 14–16, 51]. The cost and HCRU impact of ASCS in burn treatment was initially assessed using the Burn medical counter measure Effectiveness Assessment of Cost Outcomes Nexus (BEACON) model [11]. Model development was led by a group of burn experts, who incorporated diverse data streams and clinical experiences from USA-based burn centers. The model included a sequential decision tree structure that simulated an acute burn care pathway and was used to evaluate the cost effectiveness of ASCS; the initial assessment also included a budget impact analysis. The evaluation was conducted from a hospital perspective and patients with FT/mixed depth or DPT burns receiving ASCS ± STSG or SoC STSG alone were considered. Clinical inputs and the impact of ASCS on LOS were derived from clinical trials, RWD, the American Burn Association's (ABA) National Burn Repository Database, and interviews with burn surgeons. HCRU data and unit costs were derived from three US burn centers. The results of the analysis showed that across typical patient profiles and scenarios, ASCS was cost saving or cost neutral and associated with reduced LOS (up to 28 fewer days for FT/mixed-depth burns), fewer definitive closure procedures (1.5–2.8 fewer), and lower rehabilitation costs (approx. 20% lower) than STSG. Additionally, use of ASCS was estimated to reduce overall costs by 14.0–17.3% annually, with reductions in LOS contributing to approximately 70% of these savings. The study results were sensitive to, yet remained robust across, changing assumptions related to both LOS and procedure time/number.

Once again using the BEACON model, a benchmarking analysis was conducted that incorporated patient, HCRU, LOS, and cost data from a more contemporary sample of 14 US burn centers [15, 51]. Similar to the initial economic evaluation, this analysis found ASCS + STSG to be cost saving versus STSG for both FT and DPT burns across all TBSA ranges. Cost savings increased with increasing burn size as a

result of a lower number of autograft procedures, reduced LOS, and lower costs associated with ASCS. For patients with FT injuries, HCRU reductions ranged from 0.42–28.2 days (2–47%) for LOS and 0.2–2.8 (17–74%) for number of grafting surgeries for 10% to 40% TBSA wounds. As in the first BEACON analysis, rehabilitation costs were reduced by more than 20% (22.4%). Total cost savings ranged from $2130 to $311,652 (1–43%) for 10% and 40% TBSA wounds, respectively. On average, ASCS was estimated to reduce overall burn center costs by $15.8 million and per-patient costs by $79,500 (a 17.4% reduction) for a hypothetical burn center with an average of 341 patients.

Two RWD analyses have further examined the health economic impact of ASCS in burn treatment, reporting outcomes that support the validity of the BEACON model analyses [14, 16]. These studies leveraged data from electronic medical records (January 2019–August 2020) from 500 USA-based healthcare facilities. These records were used to identify adult patients receiving inpatient burn treatment with ASCS ± STSG and to match them to patients treated with STSG alone. On the basis of the initial BEACON model analysis [11], LOS was assumed to represent 70% of total costs and used as proxy to assess the dataset. In the first analysis, which examined 81 matched patients with less than 10% to less than 49% TBSA wounds, LOS was lower with ASCS ± STSG than STSG alone for almost all (four of five) TBSA intervals examined [16]. Across all patient matches (N = 81), a 13.2% reduction in LOS was observed. This reduction in hospital stay was associated with a bed cost savings of $25,864 per ASCS-treated patient; overall cost savings were $36,949 per patient. The lower LOS with ASCS ± STSG also translated into an increased hospital capacity of 2.2 inpatients/bed annually. The second analysis, which focused on patients with small burns (< 20% TBSA, which represent > 90% of burn injury hospital admissions [19]), showed similar LOS and cost benefits with use of ASCS ± STSG over STSG [14]. Across 64 matched patients, a 10.2% reduction in LOS was observed with ASCS ± STSG, leading to bed cost savings of $15,587 per patient; overall cost savings were $22,268 per patient treated with the approach. The reduced LOS translated into an increased capacity of 2.0 inpatients/bed annually. In both analyses, the cost savings associated with ASCS ± STSG more than covered the cost required for acquisition of the RECELL device.

Collectively, the results of these health economic analyses showed that regardless of burn injury size, use of ASCS ± STSG was associated with reductions in LOS and other HCRU types that in turn led to reduced bed and total healthcare costs and increased inpatient capacity for treating hospitals. It is prudent to note that in each analysis, LOS costs were calculated before the arrival of the COVID-19 pandemic, after which staffing costs increased substantially. This suggests that even greater savings may be realized with use of ASCS in today's healthcare systems.

HEALTH ECONOMIC EXPECTATIONS FOR ASCS IN TREATMENT OF FT SKIN DEFECTS

Considering the parallels in the clinical features, treatment, and challenges associated with FT thermal burn and non-thermal FT skin wounds, it may be reasonable to expect improvements in HCRU and cost savings with use of ASCS + STSG for FT skin defects on the basis of the economic evidence in burns. Both wound types can be similarly difficult to manage in terms of limited availability of healthy, harvestable donor skin and donor site morbidity; however, in clinical trials, use of ASCS + STSG significantly reduced donor skin requirements for both indications [12, 13]. As reduced donor site size can lessen associated morbidity, the need for multiple donor skin harvests, and in turn potentially improve LOS, use of ASCS for FT skin defects may also drive cost savings related to daily bed costs and other wound treatment and rehabilitation needs. Importantly, patients may also be able to return to work sooner. In any disease setting, selection of the best available treatment options and reduction of LOS leads to improved healthcare

system capability and capacity, characteristics that have proven essential during times of disaster response. Although formal economic analyses are still needed to fully elucidate the potential HCRU and cost benefits of ASCS + STSG in FT skin defects, the authors expect that savings will also emerge for this indication. It should be noted, however, that the upfront cost of the RECELL device may preclude adoption at some centers, even in light of the anticipated cost benefits.

CONCLUSIONS

Conventional management of FT thermal and non-thermal FT skin defects that involves STSG is associated with several challenges, which primarily relate to the need for creation of an iatrogenic donor skin wound. In the setting of burn treatment, clinical studies and economic analyses show that ASCS ± STSG is associated with advantages over conventional STSG for donor skin sparing, HCRU, and costs. These benefits are achieved without compromising wound healing, scarring, or patient safety. Clinical data for reconstruction of non-thermal FT skin defects now also show favorable outcomes with ASCS + STSG over conventional STSG for donor skin sparing, with comparable findings for healing, scarring, and safety. It is anticipated that this benefit will have a similarly positive economic impact on healthcare systems and patients. Future evaluations using modelling analyses and/or RWD will reveal the full HCRU and cost impact of the RECELL System in this novel indication.

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Declarations

Conflicts of Interest. Steven A. Kahn has served as a consultant to and/or speaker for AVITA Medical, Vericel Corporation, Integra Life Sciences, Medline Inc., Ex Surco, and Lumenis Inc. He has conducted research for AVITA Medical and participated on advisory panels for Vericel Corporation and Mallinckrodt. Jeffrey E. Carter is a consultant to SpectralMD Inc. and AVITA Medical. He is a stockholder of PermeaDerm Inc. & SpectralMD Inc. and has research supported by Spirit of Charity Foundation Burn Research Fund. Shelby Wilde, Aleisha Chamberlain, Thomas P. Walsh, and Jeremiah A. Sparks ae employees of AVITA Medical, Valencia, CA, USA.

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