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Accelerated re-epithelialization of partial-thickness skin wounds by a topical betulin gel: Results of a randomized phase III clinical trials program

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ABSTRACT

The clinical significance of timely re-epithelialization is obvious in burn care, since delayedwound closure is enhancing the risk of wound site infection and extensive scarring. Topical treatments that accelerate wound healing are urgently needed to reduce these sequelae. Evidence from preliminary studies suggests that betulin can accelerate the healing of different types of wounds, including second degree burns and split-thickness skin graft wounds.

The goal of this combined study program consisting of two randomized phase III clinical trials in parallel is to evaluate whether a topical betulin gel (TBG) is accelerating re-epithelialization of split-thickness skin graft (STSG) donor site wounds compared to standard of care.

Two parallel blindly evaluated, randomised, controlled, multicentre phase III clinical trialswere performed in adults undergoing STSG surgery (EudraCT nos. 2012-003390-26 and 2012-000777-23). Donor site wounds were split into two equal halves and randomized 1:1 to standard of care (a non-adhesive moist wound dressing) or standard of care plus TBG consisting of 10% birch bark extract and 90% sunflower oil (Episalvan, Birken AG, Niefern-Oeschelbronn, Germany). The primary efficacy assessment was the intra-individual difference in time to wound closure assessed from digital photographs by three blinded experts.

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A total of 219 patients were included and treated in the two trials. Wounds closed faster with TBG than without it (15.3 vs. 16.5 days; mean intra-individual difference = −1.1 days [95% CI, −1.5 to −0.7]; $p < 0.0001$).
This agreed with unblinded direct clinical assessment (difference = −2.1 days [95% CI, −2.7 to −1.5]; $p < 0.0001$). Adverse events possibly related to treatment were mild or moderate and mostly at the application site.
TBG accelerates re-epithelialization of partial thickness wounds compared to the current standard of care, providing a well-tolerated contribution to burn care in practice.

1. Introduction

Cutaneous wound healing is a complex biological process leading to re-establishment of the epidermal barrier. The clinical significance of timely wound closure is obvious in extensive wounds like burns, when delayed healing can lead to infection of the wound site and scarring. Topical treatments that accelerate wound healing are urgently needed to reduce these sequelae.

Growth factors, stem cells, nanoparticles, platelet-rich plasma, cold atmospheric pressure physical plasma [1] and many other topical treatments have been investigated [2–5], but none have proven effective in clinical trials and no treatment or pharmaceutical is currently available to accelerate the secondary closure of open superficial surgical sites or other partial-thickness wounds. Therefore, the current standard of care for open superficial surgical sites remains a moisture-regulating dressing, which promotes re-epithelialization by preventing desiccation [6,7].

Betulin is a pentacyclic triterpene found in the outer bark of white barked birches (*Betula*) [8]. Betulin has been reported to promote healing in a porcine ex vivo wound healing model and to modulate inflammatory mediators and promote keratinocyte differentiation and migration in vitro [9,10]. Evidence from preliminary studies suggests that betulin can improve the healing of different types of skin lesions, including second-degree burns [11] and necrotizing herpes [12]. A proof-of-concept phase II clinical study showed that topical betulin gel (TBG) consisting of 10% birch bark extract and 90% sunflower oil (Episalvan, Birken AG, Niefern-Oeschelbronn, Germany) significantly accelerates re-epithelialization of split-thickness skin graft (STSG) donor sites [13]. This water-free oleogel is thixotropic: when agitated TBG becomes less viscous making it easy to spread, and at rest it thickens again providing a stable occlusive cover [14,15]. Herein, we describe the results of a study program consisting of two related phase III clinical trials including a total of more than 200 patients confirming the clinical effectiveness and safety of TBG in healing of STSG donor site wounds.

2. Methods

2.1. Study design

The program design is consisting of two open, blindly evaluated, prospective, controlled, randomised, multi-centre phase III clinical trials, both using the same protocol. Study BSG-12 (EudraCT no. 2012-003390-26) was performed in Spain (6 centres), Greece (3 centres), Latvia (2 centres), and France (3 centres), and study BSH-12 (EudraCT no. 2012-000777-23) was performed in Germany (8 centres), Czech Republic (2 centres), Poland (1 centre), Finland (1 centre), Austria (2 centres), and Bulgaria (4 centres). The principal objective of the study was to examine the efficacy and tolerability of TBG. The primary efficacy endpoint was the intra-individual difference in time to wound closure (≥95% epithelialization) between two equal halves of STSG donor site wounds treated with either a standard moist wound dressing alone or a standard moist wound dressing containing TBG. The assessment was based on photo evaluation by a remote panel of three blinded experts. Study protocols were approved by the local or regional ethics committee for each centre (for the leading study centres: Ethic Committee of the Greifswald University Medicine, Greifswald, Germany and Ethic Committee of Vall d'Hebron University Hospital, Barcelona, Spain) and the studies were performed in compliance with International Conference on Harmonisation guidelines for Good Clinical Practice and the principles in the Declaration of Helsinki. All investigators and study team members received training in the study protocol and in the standardized acquisition of photographs. Informed consent was obtained from patients before inclusion in each study.

2.2. Patients

Adults with STSG donor site wounds ≥15 cm^2 and ≥3 cm wide were considered for enrolment. As a routine safety measure all study participants had to be using a highly effective method of birth control. Exclusions included skin disorders that could affect the outcome of the trial; clinically significant hypersensitivity to any of the treatments used in the trial; multiple allergic disorders; or other diseases or conditions that could interfere with the study assessments. Women could not be pregnant or breastfeeding.

2.3. Interventions

Prior to STSG surgery, the donor site was divided into two equal halves. After STSG harvest and marking of the wound halves, an overview photo was taken with a digital camera using the same standard settings at all participating centres. Once the overview photo was uploaded, the two wound halves were randomised 1:1 to TBG (other names: Oleogel-S10, Episalvan) combined with a non-adhesive moist wound dressing as