











Treating severe junctional epidermolysis bullosa with artesunate

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Severe junctional epidermolysis bullosa (sJEB) is a rare genetic, often post-partum lethal epithelial disease that is predominantly caused by biallelic non-sense/premature termination codon (PTC) sequence variants in the *LAMB3* gene [1]. *LAMB3* gene encodes the $\beta 3$ chain of the trimeric, hemidesmosomal skin anchor protein laminin 332. PTC mutations prevent the synthesis of full-length functional proteins, and truncated laminin $\beta 3$ (lam $\beta 3$) prevents the formation of laminin 332, with devastating clinical manifestations. These include generalized blistering at birth, periorificial erosions around the mouth, eyes, and nares, significant loss of mucosal surfaces of inner organs, hoarse cry, cough and respiratory difficulties. Sepsis and general failure to thrive result in the demise of patients in early infancy [2]. The condition is currently incurable and would require long-term systemic correction. Artesunate is an FDA-approved, bioavailable small molecule drug for systemic treatment of malaria [3]. It is primarily effective in the blood compartment and can be administered intravenously or orally with minimal side effects. Artesunate is a derivative of artemisinin, a compound originally isolated from the plant *Artemisia annua*. Its mode of action primarily involves the generation of reactive oxygen species (ROS) within the malaria parasite *Plasmodium*. It is targeting the parasite's haemoglobin digestion process inside red blood cells. The drug is activated by the iron present in the heme (from broken-down hemoglobin) and forms free radicals which damage the parasite's proteins and lipids, leading to its death [4].

Targeted ribosome editing in yeast and human cells identified artesunate as an efficient enhancer of lam $\beta 3$ protein translation [5–8]. Here, application of artesunate to both sJEB-LAMB3 HaCat model cells and to immortalized sJEB-LAMB3 patient keratinocytes revealed a significant increase of lam $\beta 3$ protein after 4 days of treatment with 1 μ M artesunate/0.01% DMSO in CnT Prime medium (Fig. 1). Thus, we describe the use of artesunate in a patient with sJEB, homozygous for a *LAMB3* PTC mutation. A girl of 3 months of age was

presented to the clinic with the phenotype of sJEB. In addition to widespread chronic wounds, she had growth retardation, anemia, and repeating episodes of infections (i.e., respiratory infections, bacterial wound infections, candida infection in oral mucous membranes). Since birth, her wounds were treated with various wound dressings, that were adjusted to the local condition. In general, for this indication, no approved treatment is available. Therefore, the parents agreed to start the off-label treatment with artesunate.

Artesunate was administered initially in calendar week (cw) 39 2023 intravenously with a total amount of 3 mg q.d., then switched to an oral application with 10 mg daily (1 ml of 10 mg/ml oral suspension) and increased to 20 mg after 3 months and to 40 mg after 6 months (Table 1). Artesunate was well tolerated; side effects resulting from anemic episodes most likely due to iron

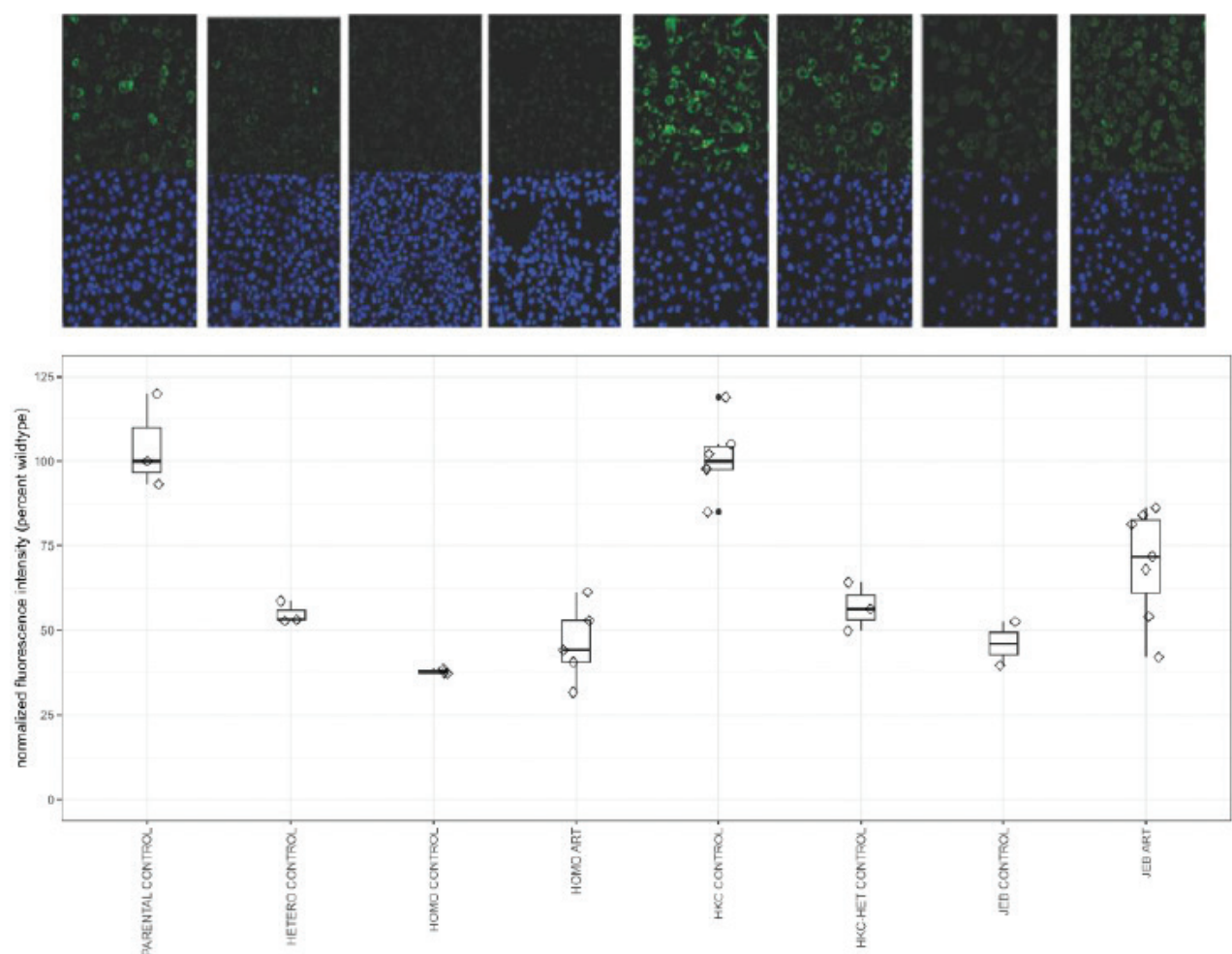


Figure 1. Immunofluorescence (IF) analysis of keratinocytes stained with α -laminin β 3 antibody. HaCat model cells comprise samples PARENTAL CONTROL (original HaCat keratinocytes), HETERO CONTROL and HOMO CONTROL, where homozygous and heterozygous deficiencies in *LAMB3* expression were generated using CRISPR/Cas9 [7]. HOMO ART, a homozygote-deficient *LAMB3* R635X cell culture was treated with artesunate 1 μ M for 4 days. Samples of E6/E7-immortalized keratinocytes were derived from cells isolated from an unaffected proband, HKC CONTROL, from a *LAMB3* R635X heterozygous carrier, HKC HET CONTROL, and from the homozygous patient, JEB-CONTROL, and from cells isolated from the patient treated with artesunate 1 μ M for 4 days, JEB-ART (p-value JEB-control vs. JEB-ART: 0,053). Scale bar: 100 μ m.

deficiency and chronic disease were met with discontinuing treatment. Clinical response showed a mixed picture: During the first 5 months of treatment, no effect on wound healing (nates and flanks) was observed according to the treating physician's assessment. An immunofluorescence (IF) investigation of patient skin was performed after these 5 months of treatment and showed only a marginal increase in expression of lam β 3 protein (Fig. 2). However, respiratory complications improved with the start of oral administration (cw 41) and returned when oral treatment was paused during infectious episodes. From December 2023 to January 2024, artesunate was also administered topically (10 mg/ml) q.d. to the affected areas on the flanks with no signs of re-epithelialization (not shown). After 6 months, oral dosing was increased to 40 mg daily. After one week of treatment at this dosage, the patient's wounds on the nates began to show gradual healing (Fig. 3). However, the patient's general condition worsened, and she died in cw 19 2024.

Table 1. Timing and dose of artesunate at 10 mg/ml preparation (cw: calendar week).

calendar week	dosage artesunate	complications
cw 39 2023	300ul iv	
cw 41 2023	1 ml orally	
cw 51 2023	2 ml orally, 4 ml topically	
cw 3 2024	break, restart afterwards with 2ml orally	episode of oral Candida
cw 8 2024	break, restart with 2ml orally	fever, anaemia
cw 12 2024	4 ml orally, amnion-transplant	

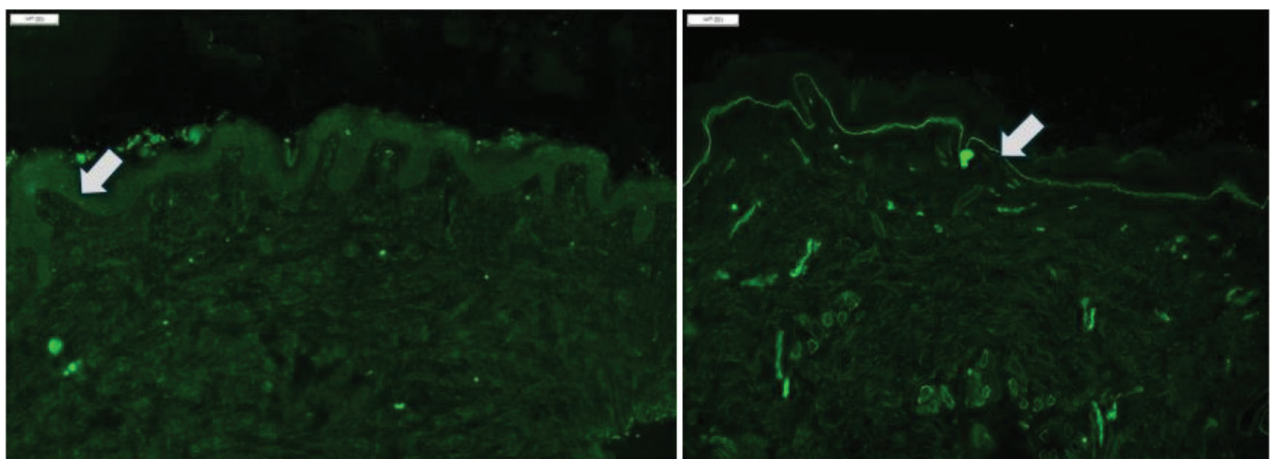


Figure 2. Immunofluorescence investigation of patient skin (biopsies taken from the right upper thigh): Residual expression of laminin β 3 after a total of 5 months of treatment, of which the last 2 months were dosed with 20 mg orally daily (left); compared to laminin α 3 expression of the patient skin (right), see white arrows. Scale bar: 100 μ m. IF images were split into green and blue channels. In the blue channel, DAPI-stained nuclei were counted using an Otsu binarization algorithm. The green channel was background corrected for non-specific lam β 3 staining using a rolling ball algorithm, followed by integration of the pixel intensities. Values were normalized by dividing the integrated intensity by the number of nuclei counted (normalized integrated intensity). Normalized integrated fluorescence intensities were divided by the mean normalized fluorescence intensities of the overall controls (parental control for the three left columns, HKC-control for the three right columns). Representative green and blue channel images are shown for each group.

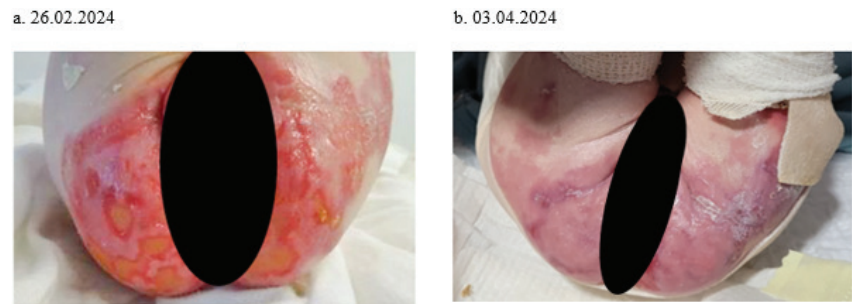


Figure 3. Wound healing during treatment with 40 mg artesunate orally daily for 1 week starting in cw 13 2024 (right) compared to cw 9 2024 at 20 mg orally daily (left).

Discussion

Biochemical and *in vitro* evidence suggests that the specific binding of artesunate to ribosomal LP35 leads to stop codon readthrough in the premature termination stop codons of the *LAMB3* gene. Here, a patient with s-JEB-*LAMB3* was treated with intravenous, oral and topical artesunate to determine safety in neonates. Safety was acceptable, and in areas where artesunate had local access (oral cavity, perianal), positive clinical effects were reported by treating physicians and visually documented (Fig. 3). Other systemic treatments for s-JEB include aminoglycosides, such as gentamicin [9], and non-aminoglycosides, such as ataluren [10], to promote general ribosomal readthrough. Gentamicin is not available orally and treatment options are limited to pulsed, short-term intravenous applications due to nephrotoxic and ototoxic effects. Ataluren is available orally, but there are no safety studies on long-term use in EB of this compound. Both compounds are compromised by their lack of specificity, i.e. they are general PTC readthrough drugs that are unable to distinguish between PTC signals resulting from mutations and endogenous PTC signals that regulate the production of protein isoforms. Possible reasons why the clinical outcome in this patient could not be changed include: 1) Bioavailability of artesunate in the skin as opposed to the blood system. 2) The initiation and dosage of treatment, which probably preclude the timely accumulation of laminin $\beta 3$ protein in epithelial tissues. 3) Effects of prenatal loss of laminin $\beta 3$ [11] leading to immune dysregulation. Future studies that treat patients as early as possible to reduce the formation of large wounds and promote the formation of intact oral and intestinal mucosa, as well as strategies to develop artesunate derivatives with improved bioavailability, are warranted.

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Additional information

Conflict of interest

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Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that experiments on humans or human tissues were performed for the present study.

For the generation of cell lines, tissue samples from healthy donors and the JEB patient were obtained upon written informed consent at the Department of Dermatology and Allergology, University Hospital Salzburg. Ethical approval was granted by the ethics committee of the county of Salzburg (vote number: 415-E/2118/45-2024). All procedures described in this study were in full accordance with Austrian legislation and with the Declaration of Helsinki.

The authors declared that no experiments on animals were performed for the present study.

Use of commercially available immortalised human and animal cell lines: HaCaT, Cell Lines Service GmbH, 300493 <https://www.selectscience.net/product/hacat>.

Use of AI

No use of AI was reported.

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Author contributions

All authors have contributed equally. We thank the patient's parents for granting permission to publish this information.

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Data availability

All of the data that support the findings of this study are available in the main text.

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