Steno Diabetes Center Copenhagen
Complications Research

UNIVERSITY OF COPENHAGEN

REGION

Novel Topical Allogeneic Bone-Marrow Derived Mesenchymal Stem Cell treatment of Hard to Heal Diabetic Foot Ulcers

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BACKGROUND

The lifetime risk of incurring a diabetic foot ulcer (DFU) for a person with diabetes is 19-34%[1] and the presence of a DFU increases the individual's five-year mortality to that of most common cancers[2] or a 2.4 times higher 5-year mortality than a person with diabetes and no DFU[3]
One of the emerging treatment options for DFUs is stem cell treatment. The pluripotent nature of stem cells makes them prime candidates for repair of all layers of the healthy epidermis, dermis and subdermal structures that are potentially disturbed by the DFU. Several potential sources of stem cells are available but especially bone marrow derived stem cells (BMMSC) has enjoyed increasing attention and DFU treatment with BMMSC has shown promise [4-9].

AIM

The aim of this phase 1b trial set out to investigate the feasibility and safety of a topically applied allogeneic bone marrow derived BMMSCs seeded in a collagen scaffold for treatment of DFUs.

Table 1.

	Patient 01	Patient 02
Age (years)	>65	>65
Diabetes Type	T2DM	T2DM
Diabetes Duration (years)	12	6
BMI (kg/m^2)	23.9	29.0
Smoker	No	Ex
Sys. Blood Pressure (mmHg)	150	108
HbA1C (mmol/mol)	57	93
eGFR (ml/min)	83	99
UACR (mg/g)	27	20
LDL (mmol/l)	1.8	0.3
Vib sens. (V) (right/left)	37/42	50/50
Monofilament Sensation (right/left)	Neg/Neg	Pos/Pos
Palpable Foot Pulses (right/left)	Yes/Yes	Yes/Yes
Toe Blood Pressure (right/left)	84/79	46/76
Offloading	Air-cast Rocker bottom sandals Individual inlays	Air-cast Rocker bottom sandals Individual inlays

METHODS

The study was performed as a prospective single center study. Between Aug. 1st 2018 and Aug. 30th, 2019, individuals with diabetes and a DFU were identified and included from our outpatient clinic.
Participants who meet in- and exclusion criteria where subsequently enrolled. After a run-in-period individuals with persistent DFU were treated with a one-time application of topical BMMSC formulation. Following BMMSC application participants were followed closely for 24 weeks. During follow-up incidence and causality of adverse events (AE) and serious adverse events (SAE) and DFU healing was monitored closely.

The applied BMMSC formulation was manufactured at Leiden University Medical Center. The investigated medical product was an Allogeneic Cellular Therapy product containing CD362 enriched Mesenchymal stromal cells from adult bone marrow (REDDSTAR ORBCEL-M, Orbsen Therapeutics Ltd. Galway, Ireland). Bone marrow was acquired from healthy non-related and leukocyte antigen (HLA)-unmatched donors. The mesenchymal stromal cells were suspended in a HypoThermosol formulation (Biolife Solutions Inc. Bothell, Washington, USA).

After application of BMMSC formulation ulcer and formulation was covered with a foam bandage and several layers of gauze. Bandages were inspected in home by homecare nurse at day three and at 1 week by scientific staff in our outpatient clinic. Subsequent choice of bandage was decided by attending educated scientific staff.

In addition to standard ulcer treatment in the form of debridement and choice of bandage, control and adjustment of offloading devices was performed by podiatrist in the outpatient clinic.



Figure 1 Clinical photo of applied BMMSC formulation

RESULTS

Of 16 identified candidates, six were included but only two fulfilled criteria for intervention. Both participants were male and had type 2 diabetes (T2DM) for 12 and six years respectively (for further baseline characteristics and ulcer characteristics see Table 1. Participants incurred four and three AEs and one and zero SAEs, respectively. Of the incurred adverse events only one AE (incurred by both participants) was suspected to be connected to the applied BMMSC treatment. The AE suspected to be associated to the BMMSC treatment was increased exudation from the treated ulcer following application. The increased exudate was resolved within one week, did not lead to other complications and did not reoccur during follow-up for either patient.
None of the treated index ulcers healed during follow-up

DISCUSSION AND CONCLUSION

In this study we present data on safety and tolerability of a novel BMMSC treatment applied to DFUs of two participants with T2DM. None of the treated ulcers healed during follow-up. However, this study was not powered to evaluate healing of DFUs, but rather safety profile of the novel BMMSC treatment. In the current study we found one AE, that both study participants experienced i.e., short-term increased exudate from the treated ulcer. The AE could be associated to the treatment with the topically applied BMMSC formulation and is potentially serious as increased exudate can lead to maceration of ulcers which is detrimental to ulcer healing. However, the AE was resolved within one week, and can easily be remedied by either choosing other bandages with higher absorption capacity or changing bandages more frequently the first week after application.
Treatment of DFU with BMMSC is not available to the general public, as the treatment often requires a large setup and an invasive procedure to extract cells, which carries a risk of complications, in addition to most BMMSC treatments being administered via injections The formulation investigated here can potentially solve these challenges as it is harvested and prepared off site from healthy donors, and delivered in ready to apply format, that is applied topically with no invasive procedures performed.
Larger clinical studies are still needed to clarify the clinical potential of treating DFUs with BMMSCs.

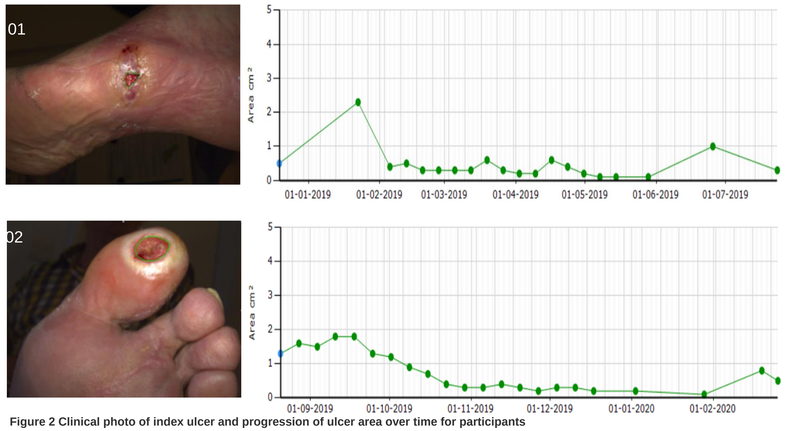


Figure 2 Clinical photo of index ulcer and progression of ulcer area over time for participants

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