A multicenter, double blind, randomized, comparative clinical study to evaluate the efficacy and safety of diperoxochloric acid (DPOCl), a wound healing solution, in patients with chronic diabetic foot ulcer

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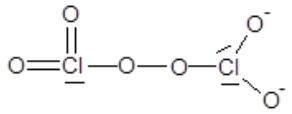
Introduction

Diabetic foot ulcers (DFU) and resulting amputations are important sequelae of diabetes mellitus. Despite an increasing number of treatment options for DFU, there is "… limited evidence to justify change in routine clinical practice and that there are no good studies to support the use of topical applications or dressing products" (Game et al., 2016). Thus, there is still an unmet medical need for new or additional therapy to prevent amputations of the lower leg.

A clinical study was conducted to investigate, whether the new solution diperoxochloric acid (DPOCl) shows clinical efficacy and safety in comparison to 0.9% physiological saline solution after administration into an un-healing, open DFU.

Study drug

DPOCl, diperoxochloric acid (DermaPro®) is a new chemical entity supporting proliferation of fibroblast cells and exhibiting strong bactericidal properties against Gram-negative and Gram-positive bacteria in cell cultures. The active component in solution is the di-anion of diperoxochloric acid, $Cl_2O_6^{2-}$.



Pharmacokinetics

In the biological environment, DPOCl degrades rapidly into the constituent parts and therefore it has not been possible to measure DPOCl in blood or tissue.

Toxicology

DPOCl did not exhibit any toxicity following acute and sub-chronic administration to mice and rats or to beagle dogs. There were no systemic intolerance reactions or skin reactions in rabbits exposed for 4 hours to 0.5 mL DPOCl.

Clinical Study

This clinical study was designed as a multi-centre, double blind, randomised, parallel group comparison between 1.2 mM DPOCl and 0.9% saline solution. The study medications were administered locally to wounds by means of a soaked gauze in a volume of approximately 0.2 ml per cm^2 wound area per day for a maximum of 90 days.

Patient population

Male and female patients, aged 18 to 80 years were recruited into the study with a DFU of 1.5 to 3.5 cm in diameter, wound stage Wagner 1 or 2, Armstrong A-C*, unsuccessfully treated for at least 6 weeks.

Diabetes mellitus had to be controlled (HbA1c ≤ 9.5%) and lower leg had to have an adequate perfusion. Local antibiotic therapy, bone infection, osteomyelitis and severe peripheral arterial occlusive disease led to exclusion.

Efficacy results

A total of 72 patients were enrolled at 10 study sites and received at least one dose of the study medication, 34 in the test group (treatment with 1.2 mM DPOCl solution) and 38 in the reference group (treatment with 0.9% (physiological) saline solution).

The **primary endpoint** for efficacy was the *reduction of wound measure area after 30, 60 and 90 days of treatment.*

- In the intention-to-treat-population (ITT), the mean wound size in the DPOCl group decreased from 2.52 cm^2 (baseline) to 1.35 cm^2 (day 30), 1.01 cm^2 (day 60) and 0.67 cm^2 (day 90).
- Reductions in the reference group were less pronounced over time (3.78 cm^2 at baseline, 3.14 cm^2 at day 90).
- The difference between test and reference group was statistically significant (p=0.0024), see Fig. 1. Significant effects were also observed for the per-protocol-population (PP) (p=0.0052).

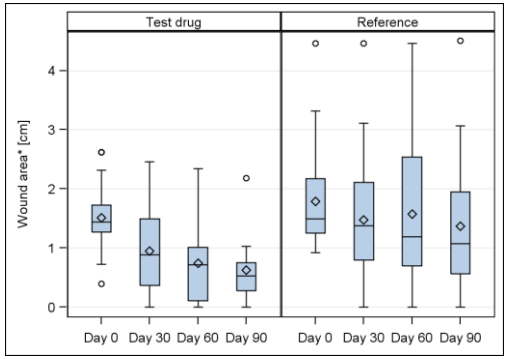


Fig. 1: Wound area* [cm] by visit (ITT)
* Square root of wound area

Secondary endpoints

For the relative frequency of patients with a reduction in wound area to 50% or more of the initial value, the results are also in favor of the DPOCl group: 63% vs 31.4% at day 30 (p=0.013), 90% vs 41.7% at day 60 (p=0.001) and 92.3% vs 60.0% at day 90 (p=0.042), see Fig. 2.

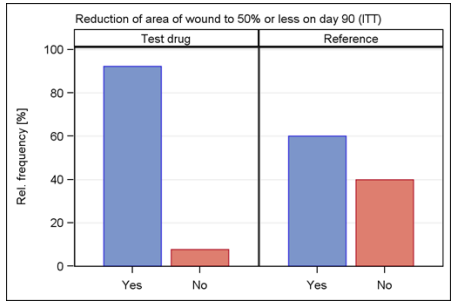


Fig. 2: Fraction of patients with reduction of wound size of ≥ 50% at day 90 (ITT)

For the secondary endpoint *time to achieve a wound closure of at least 50%*, 26.2 days were found for the DPOCl group compared to 33.8 days for the reference group. This 22.4% difference was statistically significant (p<0.001 for Log-Rank test for equality of Kaplan Meier "time to event" between treatments), see Fig. 3.

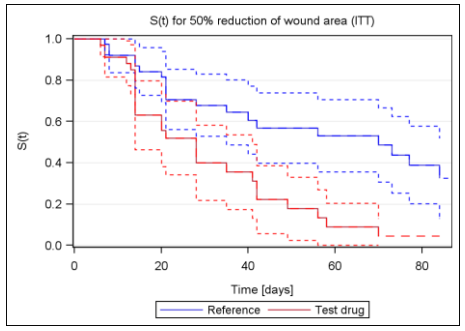


Fig. 3: „Survival"-curves related to the event „reduction of wound area to 50% or less (ITT)

Concerning the secondary endpoint *complete wound closure*, the observed difference between the treatment groups was 14.6% in favor of the DPOCl group in the ITT population (DPOCl: 38.2%, 13 patients, reference: 23.7%, 9 patients; not statistically significant (χ^2 test: p=0.181)).

There was no difference between *the mean time to complete wound closure*: DPOCl group (48.1 days, n=13); reference group (45.6 days, n=9)

Safety results

A total of 53 AEs were reported in 33 (45.8%) of the 72 patients of the Safety Analysis Set. The number of patients with at least 1 AE was comparable between the DPOCl and the reference group. Most treatment-related AEs (35.8%) were classified by the MedDRA term "skin ulcer" or by "wound complication".

A total of 9 SAEs were documented in 8 (11.1%) of the 72 patients in the Safety Analysis Set, 3 SAEs (in 3 patients) in the DPOCl group and 6 SAEs (in 5 patients) in the reference group. All SAEs except two were resolved by the end of the study.

Conclusion

The efficacy results of the present study are in line with the results obtained in case studies and demonstrate a convincing efficacy of DPOCl in the treatment of chronic DFU. In both treatment groups, wound size reduction and a complete healing of wounds were observed, though DPOCl treatment showed over time an increasing superiority over the reference treatment. The preclinical safety profile of the DPOCl solution was confirmed in the present study being comparable to the profile after the treatment with physiological (0.9%) saline solution.

Literature

Game et al. (2016). Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. Diabetes Metab Res Rev 2016; 32 (Suppl. 1),154-168.