Comparison of Safety Profile of Venous Stasis and Diabetic Foot Ulcers in Clinical Trials at a Tertiary, Safety Net Hospital

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INTRODUCTION

Currently, leg ulcers have increased interest for research due to high financial burden on healthcare systems to manage chronic wounds. (1,2) It is necessary to maintain balance between efficient study conduct and patient safety. (3)

Venous leg ulcers (VLUs) are resulting from venous insufficiency, due to venous reflux or blockage in the venous system. Several treatment options for VLUs exist in routine clinical care, however, the most used are debridement and compression dressing. (4)

Diabetic neuropathy, which is often accompanied by peripheral arterial disease (PAD), results in diabetic wounds on the lower extremities in many patients with diabetes. In addition, there are other complications of the diabetic wounds that can increase possibility for infection such as decreased mobility of the joints in the lower extremities and issues with blood circulations due to microvascular disease. Non-healing diabetic foot ulcers (DFUs) lead to amputation in the diabetic patients. These wounds in routine clinical care are treated with off-loading and sharp debridement. Also, in the past few decades the DFUs are under investigation for many innovative, experimental biomedical products, which are currently being tested in clinical trials. (5)

The **purpose** of this study is to evaluate what adverse events are most common in diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) populations, and which patients are more susceptible to having adverse events; and develop risk and safety mitigation strategies for wound care clinical trials.

METHODS

An internal audit of 15 recently conducted prospective, randomized wound care clinical trials with 261 subject enrolled at a tertiary, safety-net hospital was performed. These studies have similar objectives, study design, criteria, and outcomes. The rate of serious and non-serious adverse events and protocol deviations was assessed and compared between two wound types: diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs). Each adverse event was classified into one of the following 10 categories to better understand the correlation between type of event and wound etiology:

Category of Serious Adverse Event
Wound Infection (target wound or other)
Infection (non-wound)
Worsening of Wound (target or other) / Wound Re-Opening
Myocardial Infarction / Cardiac Arrest
Gastrointestinal Problem
Wound Pain
Pain (unrelated to wound)
New Wound Development
Allergic Reaction
Other

A statistical comparison for adverse events between the two types of wounds was performed by utilizing unpaired Student t-test. Significance level for all analyses was defined as $p<0.05$. In this project SAS 9.4: SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for our statistical analysis.

Study	Duration	Number of Patients Consented
VLU-1	September, 2005 – April, 2008	53
VLU-2	January, 2010 – May, 2011	23
VLU-3	October, 2012 – July, 2014	40
VLU-4	December, 2012 – August, 2013	17
VLU-5	March, 2013 – April, 2015	11
VLU-6	October, 2013 – December, 2014	6
DFU-1	November, 2013 – January, 2016	24
DFU-2	May, 2014 – April, 2016	30
VLU- 7	March, 2015 – July, 2017	13
VLU-8	September, 2020 – January, 2022	1
DFU-3	February, 2016 – October, 2016	7
DFU -4	May, 2017 – April, 2018	9
DFU-5	March, 2018 – June, 2019	16
DFU-6	March, 2020 – March, 2023	6
VLU-9	October, 2021 – August, 2023	5

RESULTS

- In total 21 serious adverse events (SAEs) were observed in each wound category. (Figure 1). Overall, SAEs occurred in 22.8% of all patients enrolled in DFU studies as compared to 12.4% in VLU studies. The differences in the rate of SAEs per subject enrolled between the two different wound types were not statistically significant ($p = 0.3642$).
- The most commonly occurring SAEs in both wound indications were attributed to wound infections as shown in Figure 2, both the target and non-target wound developing in the patient, while participating in the study. Slightly higher prevalence of GI problems and worsening of target wound/ reopening was observed in the DFU as compared to the VLU population also noted in Figure 2. However, according to the findings of comparative analysis of serious adverse events, difference observed for the two wound types were not statistically significant ($p = 1.0000$).

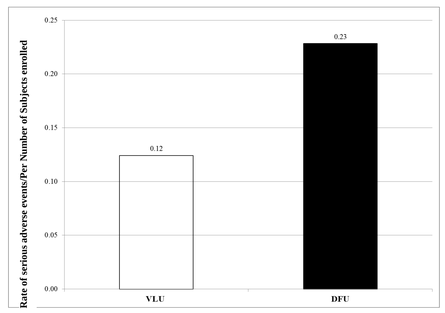

Figure 1. Incidence rate of serious adverse events (SAEs) per enrolled patient for all VLU and DFU studies analyzed in each indication.

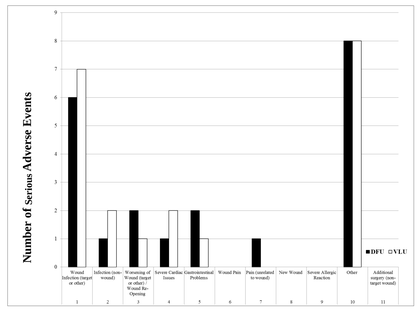

Figure 2. Serious Adverse Events by category for all VLU and DFU studies analyzed.

- The rate of non-serious adverse events (AEs) was similar at 0.8 and 0.7 AEs/patient for DFU and VLU studies, respectively (Figure 3).
- Adverse events related to wound infections, worsening of the target wound (i.e. maceration, swelling, lack of epithelization, re-opening of healed wound, etc.) and new wounds were most common in both wound types DFU and VLU (Figure 4).
- Higher incidence rate of AEs associated with wound infections 12.4% was reported in the VLU studies (21 out of the 169 enrolled subjects) as compared to DFU studies (3.3% only; 3 out of 92 subjects enrolled) (Table 4). In addition, several patients required adverse events associated with non-target wounds to be treated with surgical interventions in both VLU and DFU studies (Figure 4).
- Noteworthy, the differences in the rate of non-serious adverse events per subject enrolled between two different wound indications were not statistically significant ($p= 0.8072$).

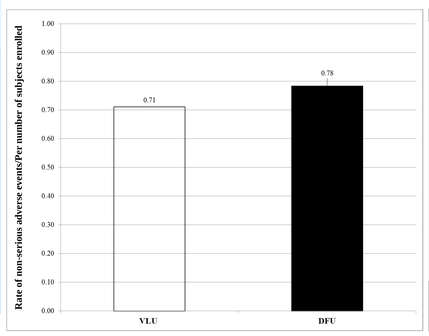

Figure 3. Incidence rate of non-serious adverse events (AEs) per enrolled patient for all VLU and DFU studies analyzed in each indication.

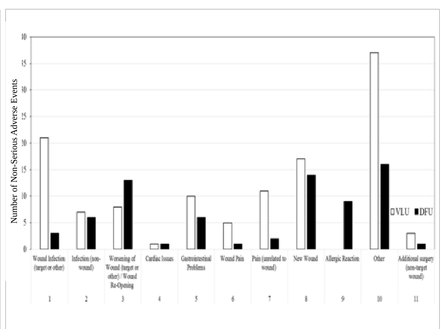

Figure 4. Cause and Effect analysis of protocol deviations in all VLU and DFU studies analyzed.

- Overall, the DFU group was noted to have higher prevalence of SAEs (22.8% of all enrolled subjects) and AEs (78.3% of all enrolled subjects) as compared to VLU group with 12.4% of SAE and 71.0% AEs observed in the study population.
- In terms of expectedness of safety issues, the SAEs (34.8%) and AEs (51.3%) in the DFU indication were more expected as compared to VLU indication, in which AEs were observed in 9.9% and SAEs in 4.6% of subjects enrolled per specific indication and were deemed as "expected". (Figure 5 and 6).

RESULTS

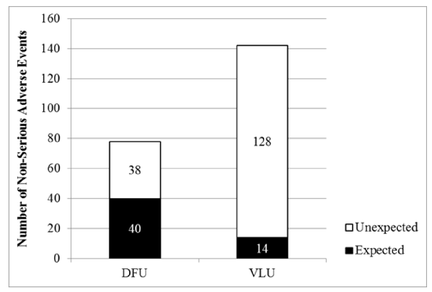

Figure 5. Expectedness of non-serious adverse events in the DFU and VLU studies analyzed.

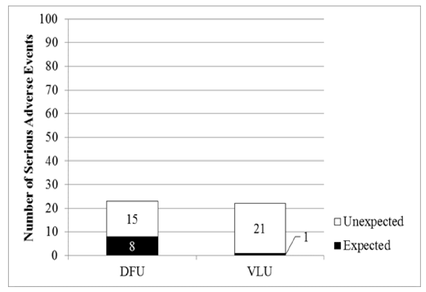

Figure 6. Expectedness of serious adverse events in the DFU and VLU studies analyzed.

- Noteworthy, "relatedness" of the adverse events to study products/procedures were determined as 0% "related" and 6.7% "possibly related" in the DFU group and 5.4% "related" and 4.2% "possibly related" in the VLU group with none of them in either group been found imposing serious safety concern on research subjects (Figure 7).

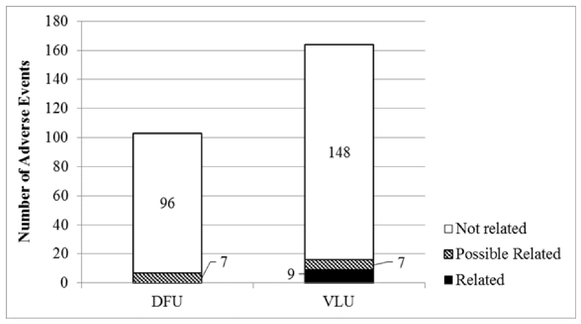

Figure 7. Relationship of serious adverse events to study product and/or study procedures for all DFU and VLU studies analyzed.

CONCLUSION

- While conducting clinical trials, an understanding of the severity, frequency and types of adverse events can help with prediction of safety profile and risk management in trials with specific wound etiology.
- An understanding of the frequency and types of adverse events can provide an expectation for those conducting trials in a particular indication, namely, that a larger number of serious adverse events per patient on average can be expected for patients with diabetic foot ulcers, and that these events will be more diverse as compared with venous leg ulcer patients.
- Overall, only 20.0% of SAEs for all studies analyzed in both VLU and DFU indications were considered as "expected" (Figure 5, 6), leaving 80.0% of all observed safety events as "unexpected". Therefore, further analysis is needed to examine patterns of safety events to determine contributing factors/causes and develop robust and efficient risk mitigation strategies, which should be specifically tailored to wound care populations.

REFERENCES

1. Leg Ulcers Clinical Trials.Gov. Clinical Trials. Retrieved June 9, 2023, from https://clinicaltrials.gov/ct2/results?cond=leg+ulcers&term=&cntry=&state=&city=&dist=
2. Chan, B., Cadarette, S., Wodchis, W., Wong, J., Mittmann, N., & Krahn, M. (2017). Cost-of- illness studies in chronic ulcers: a systematic review. Journal of wound care, 26(sup4), S4–S14. https://doi.org/10.12968/jowc.2017.26.Sup4.S4
3. Beyene R.T., Derryberry S.L. , Barbul A. The Effect of Comorbidities on Wound Healing. Surg Clin North Am. 2020 Aug;100(4):695-705. doi: 10.1016/j.suc.2020.05.002. Epub 2020 Jun 17. PMID: 32681870.
4. O'Donnell T. F., Passman M.A., Marston W.A., et.al. (2014) Management of Venous Leg Ulcers: Clinical Practice Guidelines of the Society for Vascular Surgery® and the American Venous Forum. Journal of Vascular Surgery. 60(2): 3S-59S.
5. Sinwar P. D. (2015) The Diabetic Foot Management – Recent Advance. International Journal of Surgery. 15:27-30.