Effects of Pentoxifylline on Healing Times in Diabetic Foot Ulcers
Katie Landry, DPM³; Zachary Cior, BS¹,²; Derek Talbot, DC³; Adam Fleischer DPM, MPH, FACFAS²,3,4
¹Center for Lower Extremity Ambulatory Research (CLEARY); ²Dr. William M. Scholl College of Podiatric Medicine at Rosalind Franklin University of Medicine and Science; ³Advocate Illinois Masonic Medical Center; ⁴Well Foot and Ankle Institute

Introduction
Over recent years, the number of people living with diabetes has increased in the United States and worldwide, inevitably increasing the burden to the healthcare system. The average cost for treating a diabetic foot ulcer was conservatively estimated at $30,792 per episode in 2012 [1]. Nearly 15% of all diabetics will be affected by a diabetic foot ulcer (DFU) [2]. Ulceration in diabetics results from the culmination of neuropathy, decreased vascular status, and increased chance of infection, which can occur in nearly 58% of new foot ulcers, and can foreshadow roughly 85% of people who require partial or full foot amputation [2,3]. The five-year mortality rate for patients with diabetic ulcers can be as high as 55% for ischemic related ulcers and 45% for neuropathic related ulcers [3]. With the millions of effects DFUs can have on patients and the healthcare system there is a need for treatment methods which can help improve the healing time of foot ulcers and wounds in diabetic patients.

Method
70 consecutive patients treated for DFUs from 2014 to 2019 within a large, urban-based advanced center for wound healing served as the study population. 16 patients were prescribed pentoxifylline and 54 patients were treated without pentoxifylline. Conventional ulcer treatment, which typically consisted of total contact casting and serial sharp debridement, was used on all patients irrespective of pentoxifylline regimen. The decision to start pentoxifylline was practitioner-patient dependent and, when initiated, was dosed at 400 mg three times daily. Healing rate and other covariates were obtained through chart review. Cox regression analysis was used to test for differences in healing rate while controlling for potential confounders. All patients in this study were diabetic and ulcers were scored using the WUF classification scale as outlined by Milks et al. [6]. Wounds with WUF ischemia classifications of 0 or 1 were included while dysvascular wounds (ischaemia grades 3 and 4) were excluded. Wound size and foot infection levels were not considered as inclusion/exclusion criteria. SAS version 9.4 was used for statistical analyses.

Results
Seventy patients (16 pentoxifylline, 54 no pentoxifylline) were included. The groups were similar with respect to age, duration, baseline ulcer size, comorbidities, and ulcer severity (WUF classification) at the start of treatment (p<0.05 for all). Among those patients who healed (9/16 Tx group, 39/54 control), wound healing was significantly faster in subjects receiving oral pentoxifylline in addition to conventional ulcer treatment (mean 64.87 ± 37 days versus 117.17 ± 84 days, Wilcoxon p<0.05). The probability of healing was also higher in the pentoxifylline group compared to those not receiving pentoxifylline (Figure 1 below).

Table 1. Baseline characteristics of patients within the control group and those treated with pentoxifylline 400 mg three times daily (n=70).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pentoxifylline (n=16)</th>
<th>No Pentoxifylline (n=54)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>12 (0.75)</td>
<td>34 (0.65)</td>
<td>0.3730</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.3 (9.0)</td>
<td>35.2 (15.8)</td>
<td>0.3900</td>
</tr>
<tr>
<td>WUFI</td>
<td>1.68 (0.79)</td>
<td>1.53 (0.69)</td>
<td>0.4044</td>
</tr>
<tr>
<td>Ischemia</td>
<td>0.81 (0.98)</td>
<td>0.46 (0.88)</td>
<td>0.1799</td>
</tr>
<tr>
<td>Foot Infection</td>
<td>0.75 (0.93)</td>
<td>0.51 (0.79)</td>
<td>0.3137</td>
</tr>
<tr>
<td>Wound size (cm²)</td>
<td>3.63 (7.0)</td>
<td>7.74 (21.5)</td>
<td>0.4561</td>
</tr>
</tbody>
</table>

Discussion
A recent Cochrane database review found that pentoxifylline significantly improves healing rates in patients with venous leg ulcers [7]; however, little work has been published on its efficacy in the treatment of DFUs. The analysis presented in this study suggests pentoxifylline 400 mg prescribed three times daily in conjunction with conventional ulcer treatment increases the healing time of DFUs when compared to patients undergoing just conventional ulcer treatment (mean 64.87 ± 37 days versus 117.17 ± 84 days respectively, Wilcoxon p<0.05, log-rank p<0.05). Additionally, patients were prevented from healed when adjunctively treated with pentoxifylline. Thus, it is hypothesized that DFUs burden the healthcare system with, we suspect that adding pentoxifylline 400 mg three times daily might help to reduce a patient’s time with an ulcerated foot thus ultimately decreasing morbidity, time and cost to the patient and healthcare system. Pentoxifylline is generally well tolerated, with approx. 10% of subjects reporting GI disturbances [7]. Prospective comparative work may be warranted at this time.

Acknowledgements
This project was partially supported by grant number 2T35DK074930 from the National Institute of Diabetes and Digestive and Kidney Disease. The content is solely the responsibility of the authors and does not represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.

References

Figure 1. Kaplan Meier plot demonstrating a significantly greater probability of ulcer healing among patients treated with pentoxifylline (red line) versus those not receiving pentoxifylline (blue line) (Log-Rank Chi Square 3.925, p=0.0476).

Figure 2. This patient was treated with advanced wound therapy (including total contact casting and serial wound debridement) plus PO pentoxifylline. Her time to healing was significantly decreased.