Clinical and Economic Assessment of Diabetic Foot Ulcer Debridement with Collagenase: Results of a Randomized Controlled Study☆

Arthur Tallis, DPM[1]; Travis A. Motley, DPM[2]; Robert P. Wunderlich, DPM[3]; Jaime E. Dickerson Jr, PhD[4,5]; Curtis Waycaster, PhD[4]; Herbert B. Slade, MD[4,6]; and the Collagenase Diabetic Foot Ulcer Study Group*

[1]Associated Foot & Ankle Specialists LLC, Phoenix, Arizona; [2]Department of Orthopaedic Surgery, University of North Texas Health Science Center, Fort Worth, Texas; [3]private practice, San Antonio, Texas; [4]Smith & Nephew Biotherapeutics, Fort Worth, Texas; [5]Department of Cell Biology and Anatomy, University of North Texas Health Science Center, Fort Worth, Texas; and [6]Department of Pediatrics, University of North Texas Health Science Center, Fort Worth, Texas

ABSTRACT

Background: Despite significant advances, the treatment of diabetic foot ulcers (DFUs) remains a major therapeutic challenge for clinicians, surgeons, and other health care professionals. There is an urgent need for new strategies with clinically effective interventions to treat DFUs to reduce the burden of care in an efficient and cost-effective way.

Objective: This randomized trial evaluated and compared the clinical effectiveness, tolerability, and costs of clostridial collagenase ointment (CCO) debridement to that of debridement using saline moistened gauze (SMG) and selective sharp debridement for the treatment of DFUs.

Methods: Randomized, controlled, parallel group, multicenter, open-label, 12-week study of 48 patients with neuropathic DFUs randomized to 4 weeks of treatment with either CCO or SMG after baseline surgical debridement. The primary end point was the condition of the ulcer bed at the end of treatment as measured using a standardized wound assessment tool. Secondary end points were the percentage of reduction in wound area and therapeutic response rates. Adverse events were monitored for the tolerability analysis. In addition, a comparative cost-effectiveness analysis was performed from the perspective of the Centers for Medicare and Medicaid Services as a payer.

Results: Both the CCO and SMG groups had significantly improved wound assessment scores after 4 weeks of treatment (CCO, −2.5, $P = 0.007$; SMG, −3.4, $P = 0.006$). Only CCO treatment resulted in a statistically significant decrease from baseline in the mean wound area at the end of treatment ($P = 0.0164$) and at the end of follow-up ($P = 0.012$). In addition, the CCO group exhibited a significantly better response rate at the end of follow-up compared with the SMG group (0.92 vs 0.75, $P < 0.05$). Reported adverse events were similar between the 2 treatment groups. None of the reported adverse events were considered to be related to treatment. The economic analysis indicated that the direct mean costs per responder in the physician office setting of care were $832 versus $1042 for the CCO group versus the SMG group, whereas the direct mean costs per responder in the hospital outpatient department setting were $1607 versus $1980.

*Members of the Collagenase Diabetic Foot Ulcer Study Group are listed in the Acknowledgments.

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Conclusions: CCO treatment provides equivalent debridement of DFUs similar to SMG while fostering better progress toward healing as measured by decreasing wound area over time and improved response rates at the end of follow-up. In addition, CCO yields a more favorable cost-effectiveness ratio in both the physician office and hospital outpatient department settings of care. ClinicalTrials.gov identifier: NCT01056198. (*Clin Ther.* 2013;35:1805–1820)

Key words: collagenase, cost minimization, debridement, diabetes, health economics, Medicare and Medicaid, resource utilization and costs, saline moistened gauze, ulcer healing.

INTRODUCTION

Diabetic foot ulcers (DFUs) are a frequent and serious complication of diabetes mellitus, with an annual incidence rate of 1% to 4% and a lifetime risk of 15% to 25%.[1–3] Typically, DFUs result from peripheral neuropathy and/or large vessel disease and are complicated by deformity, callus, and trauma.[1,2,4] Frequently, DFUs become infected and are a major cause of hospital admissions and lower limb amputations.[1–3] It has been reported that 40% to 70% of all nontraumatic amputations of the lower limbs occur in patients with diabetes and approximately 85% of lower limb amputations in diabetic patients are preceded by DFUs.[4–6] Often, DFU-related amputations are associated with significant morbidity and mortality, along with immense social and psychological consequences.[7,8] In addition, DFUs and related complications represent a significant economic burden that requires 20% to 40% of total health care resources spent on diabetes management.[9] The direct treatment costs of DFU (adjusted to 2012 US dollars) suggest that the mean annual costs per patient range from $5643 to $25,590 and the mean cost per patient per episode range from $9650 to $19,431.[4,10–12] The cost to treat a DFU during a 2-year period was $27,987 in 1995 and increased to $46,841 in 2009 based on the medical component of the US Consumer Price Index.[4,13]

The pathogenesis of DFU is complex and multifactorial.[14] Despite significant progress and technological advances, the treatment of DFUs is a great challenge for clinicians and other health care personnel. Debridement of the nonviable material from the DFU bed has been used for many years to enhance healing.[15–17] Debridement is thought to reduce the rate of infection and to provide an ideal healing environment.[18] There are several procedures of debridement used in the management of DFUs. These procedures include sharp surgical, enzymatic, autolytic, mechanical, and hydrotherapy.[15,16,18] Selective sharp debridement followed by saline moistened cotton gauze has been used widely in managing these wounds. This technique involves cutting away dead and infected tissue followed by daily application of saline moistened cotton gauze.[19] Dead and infected tissue adheres to the gauze as it dries. When the remoistened gauze is removed to change the dressing each day, the undesirable tissue comes with it. This action and subsequent sharp surgical debridements that are typically performed as needed in weekly visits repeatedly remove undesirable tissue.

Clostridial collagenase has been part of the armamentarium for the debridement of wounds for nearly 50 years.[20–26] During that time, numerous less specific and potentially more destructive enzymatic debriders (eg, papain/urea, fibrinolysin, trypsin, and streptodornase) have left or been removed from the market for various reasons. Collagenase is an enzyme that effectively removes detritus without harming healthy tissue. It thereby contributes to the formation of granulation tissue and subsequent epithelialization of dermal ulcers. It is possible that collagenase may help reset the conditions in the wound bed, stimulating proliferation and migration of keratinocytes and fibroblasts by rendering the wound bed permissive for migration or via the release of stimulatory peptide fragments.[27,28] Whether these effects are mediated directly by collagenase contact with cells or through byproducts of extracellular matrix digestion is not clearly understood. However, evidence supports a role for collagenase in aiding the extent and rate of wound healing.[27,29,30]

A multicenter, 12-week randomized comparative clinical trial was initiated to assess the relative effectiveness of enzymatic debridement using clostridial collagenase ointment *(CCO) with standard debridement using saline moistened gauze (SMG) and

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