Effectiveness of Platelet Releasate for the Treatment of Diabetic Neuropathic Foot Ulcers

DAVID J. MARGOLIS, MD, MSCE[1,2]
JONATHAN KANTOR, MA[2]
JILL SANTANNA, MS[2]
BRIAN L. STROM, MD, MPH[2]
JESSE A. BERLIN, SCD[2]

OBJECTIVE — The goal of this study was to specifically estimate the effectiveness of platelet releasate, a widely available treatment administered by a proprietary group of wound care centers (WCCs) for the treatment of diabetic neuropathic foot ulceration.

RESEARCH DESIGN AND METHODS — Treatment effectiveness was estimated in a retrospective cohort study controlling for treatment selection bias using logistic regression–derived propensity scores.

RESULTS — Platelet releasate was more effective than standard care. The relative risk for a wound to heal after treatment with platelet releasate compared with standard care at a WCC varied from 1.14 (95% CI 1.03–1.27) to 1.59 (1.49–1.70). The effect was greatest in those with the most severe wounds, i.e., large wounds that affect deeper anatomical structures.

CONCLUSIONS — Within the limitations of the ability of propensity score analysis to control for selection bias, platelet releasate is more effective than standard therapy. This effect is more pronounced in more severe wounds. Unfortunately, severe wounds have not been evaluated in randomized clinical trials of new interventions. We encourage the inclusion of these patients in future trials.

Diabetes Care 24:483–488, 2001

Diabetic foot ulceration is a common complication of diabetes and affects many diabetic patients in the U.S. (1). These wounds are often multifactorial in origin, but tend to occur on the plantar surface of the foot and arise in the setting of peripheral neuropathy, vascular compromise, or both. Diabetic foot ulcers are associated with increased morbidity and mortality, and they have a negative impact on both the quality of life and the productivity of diabetic patients (2,3). Studies suggest that between 25 and 50% of costs related to inpatient diabetes care may be directly attributable to the diabetic foot (4). These wounds also result in >85,000 lower extremity amputations each year in the U.S. alone (5,6). Peripheral neuropathy is an important etiological factor and has been associated as a feature in between 61 and 100% of diabetic patients with foot ulceration (6).

It is important to distinguish whether diabetic foot ulceration is associated with vascular insufficiency, because wounds caused by vascular insufficiency often require surgical revascularization. In contrast, neuropathic ulcers are amenable to medical, rather than surgical, treatment. In fact, the U.S. Food and Drug Administration (FDA) has recently approved becaplermin and one skin equivalent and is considering another skin equivalent specifically for diabetic ulceration of neuropathic origin (7–10). Becaplermin is a topical pharmaceutical also called recombinant human platelet–derived growth factor gel and has been shown to provide a modest benefit for patients with chronic neuropathic diabetic foot ulceration (7–10). Another option for treating a patient with a diabetic foot ulcer is the use of platelet releasate (PR) (11–15). PR is an autologous product offered by a group of proprietary wound care centers (WCCs) associated with Curative Health Services (CHS). Its manufacture is not difficult, and the WCCs, which are present throughout the country, market their services directly to patients and are recipients of health care provider referrals (13–15). Both becaplermin and PR are used in conjunction with standard care, which involves covering the wound with saline-impregnated gauze and instructing the patient to avoid weightbearing activities on the affected limb (16). Because it is manufactured locally, PR has not been subjected to the same FDA regulation as other wound-care products. As such, PR has not been well evaluated in a randomized controlled trial, and because so many physicians have formed an opinion regarding its efficacy, it may not be ethical to evaluate it in a randomized clinical trial (12,13,15,17). Our goal was to estimate the effectiveness of PR for the treatment of diabetic neuropathic foot ulceration. We report the relative risk of healing within 32 weeks of initiating care for patients treated at a WCC using standard wound care alone versus care that included ~20 weeks of PR.

RESEARCH DESIGN AND METHODS

We used a database maintained by CHS that includes data on ~120,000 patients with chronic wounds. A subset of 26,599

From the Departments of [1]Dermatology and [2]Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Address correspondence and reprint requests to David J. Margolis, Departments of Dermatology and Biostatistics and Epidemiology, Room 815 Blockley Hall, 423 Guardian Dr., University of Pennsylvania School of Medicine, Philadelphia, PA 19104. E-mail: dmargoli@cceb.med.upenn.edu.

Received for publication 19 September 2000 and accepted in revised form 30 November 2000.

B.L.S. and J.A.B. have received a grant from Curative Health Services.

Abbreviations: CHS, Curative Health Service; FDA, Food and Drug Administration; PR, platelet releasate; WCC, wound care center.

A table elsewhere in this issue shows Système International (SI) units and conversion factors for many substances.

patients in this database represents all patients treated between 1988 and 1997 at a CHS WCC for diabetic neuropathic foot ulceration. The reliability and validity of our ability to ascertain whether a patient has diabetic neuropathic foot ulceration and whether a wound has healed has been previously reported (18). Briefly, subjects were chosen for this study if they were patients with confirmed diabetes who had an ulcer on the plantar surface of the foot and lower limb arterial perfusion adequate for wound healing (18).

Determination of treatment status

We used the CHS database to determine whether a patient was treated with PR. Although a few patients began PR use at their first visit, 86% of the patients who were ultimately treated with PR actually received PR by the 12th week of care. Therefore, patients were dichotomized into those receiving PR by the 12th week of care and those who did not receive PR by the 12th week of care.

Study end point

We used an end point of 20 weeks after the initial 12-week evaluation period for assessing whether a patient healed. In other words, the first 12 weeks of care were treated as a run-in period (the pre-study failure period), during which time PR treatment could be initiated. Because we wanted to ensure at least 20 weeks of care with PR, our actual end point was a healed wound within the subsequent 20 weeks, i.e., within 32 weeks of care after the first WCC visit. We did this to be consistent with other studies on the efficacy of diabetic foot ulceration therapy. Many of these studies treated patients who had already failed to heal with standard therapy with an investigational agent for 20 weeks (7–10,13,15–17). To assess the effect of our choice of 32 weeks, we subsequently performed a sensitivity analysis and estimated the likelihood that a wound would heal within 26 and 29 weeks of care.

Analysis

Propensity score. Selection bias may be a major problem in using observational rather than clinical trial data, because patients are not randomly assigned to either PR or standard care. This is a limitation of case-control studies, nested case-control studies, and cohort studies. We used propensity score techniques in a cohort study to minimize selection bias. Propensity score techniques attempt to mimic the random assignment of a randomized clinical trial (19–23). Specifically, this method involves modeling the factors (covariates) that contribute to selection for treatment with PR, i.e., modeling the choice of treatment as "PR" or "no PR." A logistic regression prediction model was fitted to these covariates, thereby assigning each individual patient a modeled likelihood (propensity score) of his or her propensity to be treated with PR (19,23). This score, potential range between 0 and 1, represents a summary value of the covariates that reflects the propensity of a given patient to receive PR.

For the current study, covariates were included if they were hypothesized to affect the selection of a patient to receive PR. The following five patient variables were included in the propensity score model: age, insurance status, referral status, sex, and number of wounds. In addition, five wound variables were included in the propensity score model—duration, size, volume, debridement status, and grade (a classification tool based on depth of involved tissue). Finally, four clinic variables were also included in the model—number of patients seen at a clinic, year of treatment (as a marker for changing trends in therapy), individual center (to check for outcome differences), and clinic experience (number of years that the clinic was open). Thus, a total of 14 covariates were included in our logistic regression-based propensity score model. The ability of the model to discriminate between those who received PR and those who received only standard care within 12 weeks of care was estimated by the area under the receiver–operating characteristic curve.

Table 1—*Selected characteristics of the study population by PR status*

	No PR	PR
n	20,347	6,252
Sex (% male)	53.7 (53.0–54.4)	56.7 (55.4–57.9)
Age (years)	64.2 (64.0–64.4)	63.1 (62.7–63.4)
Wound area (mm^2)	716.4 (674.4–758.4)	981.7 (910.8–1,052.5)
Wound duration (months)	9.1 (8.8–9.5)	9.95 (9.31–10.59)
Wound grade	2.47 (2.45–2.48)	2.68 (2.65–2.70)
Wound volume (mm^3)	6,870.4 (5,155.4–8,585.3)	13,153.6 (10,914.2–15,392.9)
Insurance (%)	82.3 (81.8–82.8)	84.9 (84.0–85.8)
Clinic age (months)	36.7 (36.4–37.1)	32.4 (31.8–33.0)
Number of patients in clinic	412.8 (408.6–417.0)	500.3 (492.6–508.0)

Data are means (95% CI).

Effectiveness estimate. Patients were stratified into quintiles based on the distribution of propensity scores. χ^2 tests were used to determine the balance of covariates between the treatment groups (PR or no PR) before and after the assignment to a propensity score–based quintile.

Quintile-specific healing rates for the PR and no PR groups were calculated. The effectiveness of PR was then assessed by calculating the quintile-specific relative risk of healing at 32 weeks when using PR rather than not using PR (Mantel-Haenszel technique) (24). Before combining the quintile-specific data into a summary score, we used the Q-statistic for heterogeneity to determine whether the size of the treatment effect varied across quintiles (25).

Statistical analyses were conducted using Stata version 6.0 (College Station, TX) and SAS version 6.1 (Cary, NC).

RESULTS — Of the 26,599 study patients in the database, 21% were treated with PR by the 12th week of care (Table 1). Patients treated with PR were more likely to have larger wounds, older wounds, and wounds of higher grade, and they were treated at clinics with a larger patient census (Table 1). Each propensity score quintile contained ~5,320 patients (Table 2). Group 1 consisted of patients least likely to receive PR, whereas group 5 included those patients most likely to receive PR. The overall proportion of patients healed by 32 weeks of care showed a downward trend with the increasing group number; that is, those patients most likely to receive PR were least likely to heal independent of treatment effect (Table 3). However, treatment

Table 2—*Selected patient characteristics by propensity score quintile*

	No PR	PR
Group 1		
n	4,900	420
Sex (% male)	46.1 (44.7–47.5)	44.8 (40.0–49.5)
Age (years)	66.53 (66.13–66.93)	67.3 (66.0–68.7)
Wound area (mm^2)	189.79 (158.14–221.43)	153.04 (105.82–200.27)
Wound duration (months)	7.00 (6.44–7.55)	6.02 (4.92–7.13)
Wound grade	2.01 (1.98–2.04)	2.04 (1.94–2.13)
Wound volume (mm^3)	1,069.53 (752.44–1,386.62)	825.37 (515.41–1,135.33)
Insurance (%)	76.37 (75.18–77.56)	74.3% (70.1–78.5)
Clinic age (Months)	39.52 (38.71–40.33)	38.4 (35.6–41.3)
Number of patients in clinic	321.2 (313.6–328.8)	332.83 (305.68–359.98)
Group 2		
n	4,517	803
Sex (% male)	52.4 (51.0–53.9)	49.9 (46.5–53.4)
Age (years)	64.5 (64.1–64.9)	64.7 (63.7–65.7)
Wound area (mm^2)	237.61 (208.97–266.25)	212.48 (184.14–240.81)
Wound duration (months)	7.94 (7.35–8.54)	8.39 (6.74–10.03)
Wound grade	2.36 (2.34–2.39)	2.39 (2.33–2.46)
Wound volume (mm^3)	987.66 (828.07–1,147.24)	1,019.95 (827.92–1,211.97)
Insurance (%)	81.25 (80.10–82.39)	80.20 (77.43–82.96)
Clinic age (months)	39.63 (38.82–40.44)	40.78 (38.79–42.77)
Number of patients in clinic	372.6 (364.2–380.9)	379.87 (359.14–400.59)
Group 3		
n	4,141	1,178
Sex (% male)	56.3 (54.8–57.8)	56.4 (53.5–59.2)
Age (years)	63.7 (63.3–64.1)	64.2 (63.5–64.9)
Wound area (mm^2)	523.32 (487.18–559.46)	489.39 (441.30–537.47)
Wound duration (months)	9.43 (8.55–10.31)	9.13 (7.63–10.64)
Wound grade	2.63 (2.59–2.66)	2.63 (2.57–2.69)
Wound volume (mm^3)	3,062.8 (2,676.4–3,449.3)	4,274.31 (3,220.00–5,328.6)
Insurance (%)	83.7 (82.5–84.8)	83.2 (81.1–85.3)
Clinic age (months)	38.6 (37.8–39.4)	39.54 (37.97–41.11)
Number of patients in clinic	413.8 (404.7–422.8)	417.83 (400.58–435.08)
Group 4		
n	3,765	1,555
Sex (% male)	58.8 (57.2–60.4)	59.7 (57.2–62.1)
Age (years)	62.5 (62.0–62.9)	61.6 (61.0–62.2)
Wound area (mm^2)	1,376.8 (1,272.2–1,481.3)	1,164.14 (1,055.74–1,272.54)
Wound duration (months)	10.19 (9.36–11.02)	10.12 (8.93–11.32)
Wound grade	2.83 (2.80–2.87)	2.80 (2.76–2.85)
Wound volume (mm^3)	11,475.3 (9,797.1–13,153.4)	15,336.0 (11,384.8–19,287.1)
Insurance (%)	86.6 (85.5–87.7)	86.4 (84.7–88.1)
Clinic age (months)	36.3 (35.5–37.1)	37.4 (36.1–38.8)
Number of patients in clinic	481.3 (471.7–491.0)	489.6 (474.4–504.7)
Group 5		
n	3,024	2,296
Sex (% male)	57.9 (56.1–59.7)	59.3 (57.3–61.3)
Age (years)	62.7 (62.2–63.2)	62.1 (61.6–62.7)
Wound area (mm^2)	1,820.7 (1,574.3–2,067.0)	1,542.0 (1,367.6–1,716.4)
Wound duration (months)	12.47 (11.37–13.56)	11.52 (10.33–12.70)
Wound grade	2.70 (2.66–2.74)	2.84 (2.79–2.88)
Wound volume (mm^3)	25,017.8 (13,457.2–36,578.3)	22,805.5 (17,360.3–28,250.8)
Insurance (%)	86.4 (85.2–87.6)	88.5 (87.2–89.9)
Clinic age (months)	24.2 (23.5–25.0)	20.8 (20.1–21.5)
Number of patients in clinic	534.7 (523.2–546.3)	622.6 (611.0–634.1)

Data are means (95% CI).

groups were well balanced for the risk factor variables that we assessed after stratification (Table 2). The only exception was wound grade in the fifth quintile, which was not perfectly balanced, even after stratification. The imperfect balance for some individual covariates in the propensity score model was expected and is a feature of most propensity score models (20). The multivariable logistic regression model that was used to estimate each individual's propensity to be treated with PR had excellent discriminative ability, as evidenced by the area under the receiver–operating characteristic curve of 0.90.

Overall, 43.1% of patients healed within 32 weeks of the initiation of care, including 50% (48.7–51.2) of patients using PR and 41% (40.3–41.7) of patients not receiving PR (Table 3). The percentage of patients healed within 26 and 29 weeks of care varied little from that of 32 weeks of care (41.6 and 42.4%, respectively). Patients treated with PR were more likely to heal than those patients not treated with PR for all five propensity score strata (Table 3). However, the relative risk of healing due to PR increased consistently for wounds that were more likely to be treated with PR, increasing from 1.14 (1.03–1.27) in the first quintile to 1.59 (1.49–1.70) in the last quintile (Table 3). The test for heterogeneity was significant at $P < 0.001$, indicating that the magnitude of the effect of PR was not the same for all groups. This suggests that for patients in the high quintiles, PR treatment at a WCC is more superior than standard care.

Further ad hoc analysis showed that the effect of PR was greatest for those patients with larger wounds of higher grade, such that stratifying the patients in categories based on wound size and grade revealed a pronounced trend in the effectiveness of PR across categories. For example, for a wound of 2 cm^2, grade four (a large anatomically deep wound), the odds ratio for PR treatment–associated healing was 2.61 (2.32–2.94). In contrast, for a wound of 0.5 cm^2, grade one (a small anatomically shallow wound), the odds ratio for PR treatment–associated healing was 1.27 (1.13–1.44).

CONCLUSIONS — This study is the first independent assessment of the efficacy of PR, which has been used for >10 years on thousands of patients in the U.S. We found that PR is effective in the treat-

Table 3—*Proportion of wounds healed by PR status; relative risk of healing with PR and risk difference of healing with PR by quintile*

Group	No PR: proportion healed by 32 weeks	PR: proportion healed by 32 weeks	Relative risk of healing with PR
1	46.6 (45.2–48.0)	51.9 (47.1–56.7)	1.14 (1.03–1.27)
2	46.6 (45.1–48.0)	55.0 (51.6–58.5)	1.24 (1.16–1.34)
3	40.4 (38.9–41.9)	49.8 (47.0–52.7)	1.29 (1.20–1.38)
4	35.2 (33.7–36.7)	49.1 (46.6–51.6)	1.43 (1.33–1.52)
5	31.6 (30.0–33.3)	48.5 (46.5–50.6)	1.59 (1.49–1.70)
Overall	41.0 (40.3–41.7)	50.0 (48.7–51.2)	1.38 (1.33–1.42)

Data are % (95% CI) and relative risk (95% CI).

ment of diabetic neuropathic foot ulceration. It appears that PR is more likely to be used in more severe wounds and is more effective than standard care in these severe wounds. However, we did find a significant interaction between the effectiveness of PR and the propensity score quintile.

Most patients treated with PR do not begin this treatment at their first visit. Previous studies that examined the efficacy of treatments for diabetic neuropathic foot ulceration have often used the cutoff of 20 weeks of care (7–10). Our sensitivity analyses suggested that there was very little difference (<2%) among the percentage of patients who healed within 26, 29, or 32 weeks of care. Therefore, we used 20 weeks of care with PR (32 total weeks of care) as our study end point. In other words, patients in our trial had a 12-week prestudy observation period and then a 20-week treatment period. This is consistent with another study that suggests that the percentage of healed diabetic neuropathic foot ulceration levels off after ~20 weeks, indicating little incremental increased healing after 20 weeks.

One of the important reasons for performing a randomized controlled trial is that it can essentially eliminate selection bias, because patients are randomly assigned to treatment. Purposeful selection or selection bias refers to the likelihood that certain types of patients (such as those more or less likely to heal) are differentially chosen for treatment with PR. Therefore, the bias in an observational study, such as a case-control study or a cohort study, could be that patients treated with PR might have wounds that are more or less likely to heal than patients not treated with PR. By using a propensity score analysis in our cohort study, we attempted to control for selection bias by balancing factors between those patients who received PR and those who did not receive PR and then creating strata related to the likelihood of receiving PR. Because patient outcomes for those treated with standard therapy and PR are compared only within each quintile (within patients equally likely to receive PR regardless of whether they actually received PR), selection bias—as explained by the measured covariates—should no longer affect patient outcomes.

Propensity score techniques, as well as some large cohort studies, have several advantages over randomized controlled trials. First, propensity score analyses may be used to determine the effectiveness of treatment, whereas randomized controlled trials are used to estimate the efficacy of treatment. Effectiveness refers to the real-world ability of a treatment to provide a benefit, whereas efficacy involves the potential benefits of a therapy under idealized conditions. Because patients are rarely subjected to these idealized conditions, effectiveness estimates may be more useful than efficacy estimates when deciding the best treatment options for individual patients. Another advantage of propensity score techniques is that they permit investigators to use observational data that contain far more individual patients of greater diversity than would be possible using a large randomized controlled trial, with the exception of the infrequently used randomized simple trial design. Both of these aspects of propensity score techniques, reflecting effectiveness rather than efficacy, and the fact that they permit the use of data from thousands of patients contribute to the improved generalizability of results from propensity score analyses over those from randomized controlled trials (19).

Despite these advantages, there are several limitations to propensity score techniques. First, propensity score techniques control only for the known covariates that are included in the propensity score model (20). Thus, if we failed to include a covariate that has a substantial effect on the propensity of a patient to be treated with PR, then it is possible that the propensity for PR treatment within each quintile would not be entirely homogeneous. Covariates that were not available for analysis in this database included glycemic control, history of cigarette use, and the microbiologic status of the wound. However, because our propensity score model already had excellent ability to discriminate (area under the receiver-operator curve of 0.90) between the patients who were treated and those not treated and because PR was used in the more severe patients, our results would have been biased toward not finding an effect (the null). Another limitation of this methodology is that whereas the propensity to receive treatment is relatively stable within each quintile, it is not perfectly equal throughout the quintile; thus, differences in treatment effect could be due to subtle differences in the propensity to receive treatment, i.e., residual confounding. Also, because scores are derived from a combination of multiple covariates, the individual effect of each covariate and its contribution to the overall effect cannot be determined with statistical precision (21,22). A final limitation is that the commencement of treatment with PR is a moving target. Only those who started treatment with PR by week 12 of care were considered users of PR. Some patients did receive PR after week 12, and these would have been classified as having used only standard care, thereby biasing our effect of PR toward the null.

The generalizability of our findings to all populations of patients with diabetic neuropathic foot ulceration may be limited, because we used data from specialty wound care clinics rather than from primary care providers. Yet, given the large numbers of patients from many different geographic locations, these data are likely to be generalizable to the general population. In addition, these WCCs are widely available to patients and are frequently a source of physician referral for patients with a chronic wound.

Health care providers were not blinded to the treatment status of patients in our study. Therefore, it is possible that

patients who were treated with PR could have been treated in a systematically different way from those that were treated with standard care alone. The differential ascertainment of healing does not represent a problem, because wound healing was documented with photographs, as discussed in a previous study (18). Concerns that patients treated with PR may have received wound care that was otherwise more aggressive are not likely problematic, because covariates that would be associated with better treatment were similar for those patients who received PR and those who did not.

A patient-level meta-analysis of randomized controlled trials has suggested that wound area and wound duration are responsible for a wound being unlikely to heal within 20 weeks of care (26,27). Because of the constraints of those randomized clinical trials, wounds of higher grade were excluded from study. Therefore, in general, wounds in the current study with higher propensity to be treated with PR are more severe and less likely to heal than those less likely to be treated with PR. In fact, as seen in Table 2, more severe wounds were more likely to be treated with PR. Also, as compared with standard care, the more severe the wound (the higher the quintile) the larger the benefit of PR with respect to improving the likelihood of healing within 32 weeks of care. Consequently, based on our results, PR may be the first therapy for diabetic neuropathic foot ulceration that has been shown to improve the chance of healing for wounds that extend through muscle or wounds that are complicated by osteomyelitis (wounds of higher grade). Because these severe wounds are more likely to progress to the point that amputation is necessary, it is important that PR appears to improve the chance of healing, presumably decreasing the risk of amputation, even for patients with advanced chronic wounds. Becaplermin, of course, may have similar effects on severe wounds, but the clinical trials evaluating this topical therapy excluded patients with deep wounds (groups 3–5 in our study) (7–9).

We found that PR improves the proportion of diabetic neuropathic foot ulcers that heal after 32 weeks of care when compared with treatment using standard care alone. The relative benefits of PR over standard care persist for wounds of all sizes, and the relative risk of healing using PR versus standard care increases with wounds that are larger and more severe. In the setting of this study, these were also the patients more likely to be treated with PR. Therefore, PR represents an effective treatment for diabetic neuropathic foot ulceration. PR also appears to be effective in severe wounds, and may therefore play an important role in preventing amputation. Our findings also have implications for future growth-factor studies: instead of excluding patients with the most severe wounds, such patients should be included, because it seems that the relative effect of PR and potentially other growth factor-mediated treatments is greatest in the most severe wounds. Future studies should include and perhaps focus on those patients with the largest and deepest wounds, because these wounds are more likely to progress to amputation, and they appear to have a greater relative response to the use of PR and perhaps the use of other growth-factor therapies.

References

1. Mancini L, Ruotolo V: The diabetic foot: epidemiology. *Rays* 22:511–523, 1997
2. Phillips T, Stanton B, Provan A, Lew R: A study of the impact of leg ulcers on quality of life: financial, social, and psychological implications. *J Am Acad Dermatol* 31:49–53, 1994
3. Brod M: Quality of life issues in patients with diabetes and lower extremity ulcers: patients and care givers. *Qual Life Res* 7:365–372, 1998
4. Apelqvist J: Wound healing in diabetes: outcome and costs. *Clin Podiatr Med Sur* 15:21–39, 1998
5. National Diabetes Data Group: *Diabetes in America*. Washington, DC, U.S. Govt. Printing Office, 1995 (NIH publ. no. 95–1468)
6. Reiber GE: The epidemiology of diabetic foot problems. *Diabet Med* 13 (Supp. 1): S6–S11, 1998
7. Wieman TJ, Smiell JM, Su Y: Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: a phase III randomized placebo-controlled double-blind study. *Diabetes Care* 21:822–827, 1998
8. Steed DL: Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers: the Diabetic Ulcer Study Group. *J Vasc Surg* 21:71–78, 1995
9. Smiell JM: Clinical safety of becaplermin (rhPDGF-BB) gel: the Becaplermin Studies Group. *Am J Surg* 176 (Suppl. 2A): 68S–73S, 1998
10. Gentzkow GD, Iwasaki SD, Hershon KS, Mengel M, Prendergast JJ, Ricotta JJ, Steed DP, Lipkin S: Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care* 19:350–354, 1996
11. Moulin V, Lawny F, Barritault D, Caruelle JP: Platelet releasate treatment improves skin healing in diabetic rats through endogenous growth factor secretion. *Cell Mol Bio* 44:961–971, 1998
12. Knighton DR, Fiegel VD: Growth factors and comprehensive surgical care of diabetic wounds. *Curr Opin Gen Surg* 32–39, 1993
13. Knighton DR, Citresi K, Flegel VD, Austin LL, Butler EL: Stimulation of repair in chronic, nonhealing cutaneous ulcers using platelet-derived wound healing formula. *Surg Gyn Obstet* 170:56–60, 1990
14. Wesh WJ: Autologous platelet gel-clinical function and use in plastic surgery. *Cos Derm* 13:13–19, 2000
15. Krupski WC, Reilly LM, Perez S, Moss KM, Crombleholme PA, Rapp JH: A prospective randomized trial of autologous platelet-derived wound healing factors for treatment of chronic nonhealing wounds: a preliminary report. *J Vasc Surg* 14:526–536, 1991
16. American Diabetes Association: Consensus development conference on diabetic wound care. *Diabetes Care* 22:1354–1360, 1999
17. Miller MS: Use of topical recombinant human platelet-derived growth factor-BB (becaplermin) in healing of chronic mixed arteriovenous lower extremity diabetic ulcers. *J Foot Ankle Surg* 38:227–231, 1999
18. Kantor J, Margolis DJ: The accuracy of using a wound care specialty clinic database to study diabetic neuropathic foot ulcers. *Wound Repair Regen* 8:169–163, 2000
19. Rubin DB: Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 127:757–763, 1997
20. Joffe MM, Rosenbaum PR: Invited commentary: propensity scores. *Am J Epidem* 150:327–333, 1999
21. Rosenbaum PR, Rubin DB: The central role of propensity score in observational studies for causal effects. *Biometrika* 70: 41–55, 1983
22. Rosenbaum PR, Rubin DB: Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 79:516–524, 1984
23. D'Agostino RB Jr.: Propensity score methods for bias reduction in the comparison of a treatment to a nonrandomized control group. *Stat Med* 17:2265–2281, 1998
24. Rosner BA: *Fundamentals of Biostatistics*. Belmont, Duxbury Press, 1995

25. Hardy RJ, Thompson SG: Detecting and describing heterogeneity in meta-analysis. *Stat Med* 17:841–856, 1998
26. Margolis DJ, Kantor J, Berlin JA: Healing of diabetic neuropathic foot ulcers receiving standard treatment: a meta analysis. *Diabetes Care* 22:692–695, 1999
27. Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA: Risk factors for healing neuropathic, diabetic foot ulcers: a pooled analysis. *Arch Dermatol* 12:1531–1535, 2000