Long-term outcome study of growth factor-treated pressure ulcers

Wyatt G. Payne, M.D. a,b, Diane E. Ochs, R.N. a,b, Dessie D. Meltzer, R.N. b, Donald P. Hill, Pharm.D. a,b, Rudolph J. Mannari, P.A.-C. b, Leslie E. Robson, M.S., R.N. b, Martin C. Robson, M.D. a,b,*

aDepartment of Surgery, University of South Florida, Tampa, Florida, USA
bInstitute for Tissue Regeneration, Repair, and Rehabilitation, Department of Veterans Affairs Medical Center, Bay Pines VAMC (151W) P.O. Box 5005, Bay Pines, Florida 33744, USA

Received April 3, 2000; revised manuscript August 30, 2000

Abstract

Background: Exogenous application of growth factors have been reported in an attempt to accelerate healing of chronic wounds. Most of the trials were of brief duration with short to no follow-up periods. Long-term outcome studies are sparse for pressure ulcer therapies with success rates around 30% for both operative and nonoperative treatments.

Methods: Follow-up evaluations were performed serially up to 12 months for patients completing a 35 day blinded, placebo-controlled cytokine clinical trial of pressure ulcers.

Results: Fifty-four of 61 patients completed the follow-up period with 68.5% of the patients (37 of 54) being healed after 1 year. Of patients healing ≥85% during the active treatment phase, 84.6% were healed after 1 year compared with 61% of those that healed <85% during treatment (P <0.05).

Conclusion: Long-term outcome was better in this growth factor trial than with surgical or standard nonoperative treatment of pressure ulcers. Since only patients receiving exogenously applied cytokines achieved ≥85% closure during the treatment phase of the trial, the excellent long-term outcome appears attributable to the cytokine therapy. © 2001 Excerpta Medica, Inc. All rights reserved.

Keywords: Outcome study; Growth factors; Cytokines; Clinical trial; Wound healing

Lack of cellular and molecular signals required for normal wound repair processes such as resolution of inflammation, angiogenesis, deposition of extracellular matrix, contraction, epithelialization, and remodeling may be a major contributing factor to poor healing of chronic wounds such as pressure ulcers [1,2]. Cytokines, especially the subclass of growth factors, provide many of the cellular and molecular signals necessary for normal healing but are deficient in pressure ulcers [3,4]. Mast and Schultz [5] and Tarnuzzer et al [6] have postulated that this deficiency is due to the fact that in chronic wounds, repeated trauma, ischemia, and infection increase the level of proinflammatory cytokines, increase the level of matrix metalloproteinases (MMPs), decrease the presence of tissue inhibitors of metalloproteinases (TIMPs), and lower the level of growth factors.

Exogenous application of growth factors has been reported for the past 10 years in an attempt to accelerate healing of chronic wounds [7]. This approach appears rational for pressure ulcers as they are deficient in growth factors, and Pierce et al [8] showed that the addition of exogenous PDGF to human pressure ulcers deficient in that factor resulted in the recruited and activated wound cells synthesizing much greater amounts of PDGF. This laboratory has reported prospectively randomized, blinded, placebo-controlled trials using exogenous PDGF, bFGF, IL-1B, GM-CSF, and sequential GM-CSF/bFGF for the treatment of pressure ulcers [1,9]. Mustoe et al [10] and Rees et al [11] have also reported trials of PDGF-BB–treated pressure ulcers. Most of these trials have demonstrated safety of the growth factor and varying degrees of efficacy. However, most of the trials were of brief duration with very short follow-up periods.

Acceleration of wound closure during the period of active treatment with growth factors is not the ideal outcome measure of wound healing for a chronic wound. The Wound Healing Society has stated that acceptable healing must...
result in sustained anatomical and functional integrity [12]. Therefore, long-term follow-up and recurrence rates must factor into usefulness of a wound therapy such as growth factors. Disa et al [13] have reported that operative therapy of pressure ulcers with flaps is unsuccessful long-term with a 61% ulcer recurrence and a 69% patient recurrence within 9.3 months. This means that there was only a 31% successful long-term outcome for surgery. The best data for non-operative treatment report healing rates of 39.9% for stage III pressure ulcers and 34.1% for stage IV ulcers in nursing home patients and 45.2% and 30.6% respectively for hospitalized patients [14,15]. No long-term outcome data are available for pressure ulcers treated with exogenous application of growth factors, but Steed et al [16] did report a 68.8% recurrence rate for diabetic neuropathic foot ulcers treated with a mixture of autologous growth factors.

Most pressure ulcer clinical trials evaluating growth factors to date have been phase I or early phase II trials evaluating either safety or dose response of the applied cytokines. Long-term outcome and recurrence data have not been collected. In an attempt to gather such outcome data, a serial follow-up period was built into a prospectively randomized, blinded, placebo-controlled pressure ulcer clinical trial. The trial was designed as a four-arm trial comparing the effect of sequentially applied topical GM-CSF and bFGF therapy to each cytokine applied alone, and to the placebo vehicles [1].

Methods

Follow-up data were serially collected as part of a four-arm, blinded, randomized, pressure ulcer clinical trial comparing sequential topical GM-CSF/bFGF therapy with each cytokine alone and with a placebo over a 35-day period. Details of the clinical trial and results are published elsewhere [1]. The trial enrolled only patients with pressure ulcers involving any tissue from a bony prominence to the subcutaneous tissue (grade III/IV). Patients meeting the study criteria underwent screening, evaluation, and baseline data collection. Sharp debridement to remove necrotic tissue and to open all sinuses and tracts was then performed. Minor debridement was performed at the bedside in follow-up if necessary. Wound healing was monitored during the trial by weekly alginate molds of the ulcers [17]. After the final dose of drug on day 35, a mold impression was made on day 36 to determine the degree of healing (percent wound closure) during the active phase of the trial. The patients were then seen in follow-up at 3 weeks, 6 weeks, 3 months, 6 months, and 1 year after active therapy. At each follow-up visit the wounds were assessed as to whether they had achieved complete healing (100% closure), were still less than 100% healed, or had recurred after a time of 100% closure. Any open wounds seen during the follow-up period were volumetrically measured with alginate molds to determine percent of healing.

Differences amongst various groups in the time to achieve complete healing during the follow-up phase were determined by survival analyses using the Kaplan-Meier method [17]. Significances of differences in time to reach 100% closure was determined by the log-rank and Wilcoxon P values derived from the Kaplan-Meier method. All survival analyses were done using JMP software (SAS Institute, Inc., Cary, NC). Chi-square and Fisher exact analyses were used to compare proportions of various groups of patients healed. All proportion analyses were performed using SigmaStat software (SPSS, Inc., Chicago, IL).

Results

A total of 61 patients enrolled into this study completed the 35-day active treatment course [1]. The degree of healing on day 36 ranged from 3% to 99% wound closure (Table 1). Four patients died and 3 were lost to follow-up during the 1-year follow-up period. Partial follow-up data are thus available for 59 patients, and complete follow-up data are available for 54 patients over the 1-year follow-up period.

Thirty-seven of the 54 (68.5%) of patients were totally healed at the 1-year follow-up visit. Eight of the 17 unhealed patients had never reached 100% closure, leaving 9 of the 54 patients (16.7%) who had recurred after being totally healed at one time. There were no significant differences amongst the percentage of patients healed across the four treatment groups at any follow-up visit (P > 0.05; Fig. 1).

The time to achieve complete healing during the follow-up period for each of the four treatment groups was derived from Kaplan-Meier survival analysis (Fig. 2). Although there was a trend for the bFGF-treated patients to achieve healing faster than the other groups, there were no significant differences among the four treatment groups (log-rank $P = 0.18$ and Wilcoxon $P = 0.25$). Because during the acute treatment phase, patients who received bFGF as part of their topical treatment (the bFGF alone group and the sequential GM-CSF/bFGF group) achieved >85% and >90% closure significantly more frequently than patients in the other two groups [1], a Kaplan-Meier survival analysis was performed describing time to healing in all patients receiving bFGF as part of their treatment regimen versus those who did not (Fig. 3). Although there was a trend for the patients receiving bFGF to achieve 100% closure faster than those who did not receive bFGF, the difference was not statistically significant (log rank $P = 0.14$ and Wilcoxon $P = 0.20$).

Patients who were the best healers during the acute phase of the trial (achieving >85% wound closure in 35 days) fared significantly better during the 1-year follow-up period. Thirteen patients healed with >85% wound closure during the 35-day active treatment phase. Eleven of the 13 (84.6%) were 100% healed at the 1-year follow-up visit. This compared with 61% of patients (25 of 41) who were <85%
Table 1
Healing response during one-year of follow-up

<table>
<thead>
<tr>
<th>Subject</th>
<th>Treatment group</th>
<th>Percent healed day 36</th>
<th>Week 3</th>
<th>Week 6</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GM-CSF</td>
<td>66</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>bFGF</td>
<td>71</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>GM-CSF/bFGF</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Vehicle</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>GM-CSF/bFGF</td>
<td>98</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Vehicle</td>
<td>69</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>GM-CSF</td>
<td>66</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>bFGF</td>
<td>85</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>GM-CSF</td>
<td>63</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>bFGF</td>
<td>64</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>GM-CSF/bFGF</td>
<td>62</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>Vehicle</td>
<td>79</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>bFGF</td>
<td>98</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>Vehicle</td>
<td>82</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>GM-CSF/bFGF</td>
<td>91</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>GM-CSF</td>
<td>77</td>
<td>0</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>17</td>
<td>GM-CSF</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>bFGF</td>
<td>92</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>GM-CSF/bFGF</td>
<td>77</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>Vehicle</td>
<td>68</td>
<td>0</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>21</td>
<td>bFGF</td>
<td>74</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>22</td>
<td>Vehicle</td>
<td>76</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>23</td>
<td>GM-CSF/bFGF</td>
<td>87</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>GM-CSF</td>
<td>78</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>25</td>
<td>bFGF</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>26</td>
<td>GM-CSF/bFGF</td>
<td>65</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>27</td>
<td>GM-CSF</td>
<td>93</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td>Vehicle</td>
<td>70</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>29</td>
<td>GM-CSF</td>
<td>71</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>GM-CSF/bFGF</td>
<td>92</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>31</td>
<td>Vehicle</td>
<td>80</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>32</td>
<td>bFGF</td>
<td>94</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>33</td>
<td>GM-CSF</td>
<td>92</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>34</td>
<td>bFGF</td>
<td>79</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>35</td>
<td>GM-CSF/bFGF</td>
<td>44</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>Vehicle</td>
<td>84</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>37</td>
<td>GM-CSF/bFGF</td>
<td>83</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>38</td>
<td>Vehicle</td>
<td>72</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>39</td>
<td>GM-CSF</td>
<td>89</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>40</td>
<td>bFGF</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>41</td>
<td>GM-CSF/bFGF</td>
<td>57</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>42</td>
<td>bFGF</td>
<td>99</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>43</td>
<td>Vehicle</td>
<td>74</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>44</td>
<td>GM-CSF</td>
<td>66</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>45</td>
<td>GM-CSF/bFGF</td>
<td>73</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>46</td>
<td>bFGF</td>
<td>91</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>47</td>
<td>Vehicle</td>
<td>63</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>48</td>
<td>GM-CSF</td>
<td>81</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>49</td>
<td>bFGF</td>
<td>61</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>50</td>
<td>GM-CSF/bFGF</td>
<td>73</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>51</td>
<td>GM-CSF</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>52</td>
<td>Vehicle</td>
<td>82</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>53</td>
<td>GM-CSF/bFGF</td>
<td>73</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>54</td>
<td>bFGF</td>
<td>42</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>55</td>
<td>GM-CSF</td>
<td>70</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>56</td>
<td>bFGF</td>
<td>79</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>57</td>
<td>Vehicle</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>58</td>
<td>GM-CSF/bFGF</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>59</td>
<td>GM-CSF</td>
<td>59</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>60</td>
<td>GM-CSF/bFGF</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>61</td>
<td>Vehicle</td>
<td>68</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>E</td>
<td></td>
</tr>
</tbody>
</table>

1 = healed (100% closed); 0 = not healed (<100% closed); E = expired; L = lost to follow-up.
closed on day 35 being 100% closed at the 1-year follow-up visit. Fig. 4 demonstrates the percent of patients with totally healed wounds at each follow-up visit as grouped by healing response (≥85% closed versus <85% closed) after the 35-day active treatment period. As can be seen, there was a significantly greater proportion of healed patients at all visits in the ≥85% closure during the acute trial group (P < 0.05). When performing a Kaplan-Meier survival analysis to describe time to healing, those who healed ≥85% during the acute treatment period, healed significantly faster (log rank P < 0.001 and Wilcoxon P < 0.001; Fig. 5).

Comments

For a new treatment to be considered truly efficacious, its recipients must have a long-term better outcome. Growth factors and bioengineered devices are being investigated for the treatment of chronic wounds involving pressure ulcers.

To date, there have been no long-term outcome studies. The single long-term follow-up study for exogenous growth factor treatment of a chronic wound was by Steed et al [16] for diabetic foot ulcers. They observed patients for 30 months after a 20-week trial of topically applied growth factors that had been released from platelets. Thirty-six patients were entered in the trial and 16 healed during the 20 weeks of active treatment. Of the 16 patients whose ulcers healed, 11 (68.8%) recurred during the follow-up period. Five ulcers remained healed at 30 months. This is only 13.9% of the original 36 and 31.2% of the 16 that healed with active treatment.

The 68.5% (37 of 54) patients who were healed at the 1-year follow-up visit in the present trial is remarkable. Although no other long-term growth factor studies are available for pressure ulcers, this percentage is far greater than the literature reports for other pressure ulcer treatments. Disa et al [13] reported that only 31% of patients were cured.
long term with excision of the ulcer and pedicled flap reconstruction. Goodman et al [18] also reported that operative reconstruction was not a long-term solution for pressure ulcers. They showed that 64.6% of reconstructed ulcers recurred during a 1- to 6-year follow-up period and a total of 79.2% of patients developed recurrent or new ulcers [18]. For nonoperative therapy, Berlowitz et al [15] reported on 19,981 long-term care institutionalized patients with pressure ulcers. Reporting on a 6-month follow-up period, they found 45.2% of stage III ulcers were healed and 30.6% of stage IV ulcers. All of the ulcers in our study were stage III or IV and at the 6-month follow-up visit between 60% and 80% of the ulcers were 100% healed (Fig. 1). The figures from the present trial are also considerably higher than the 6-month healing data reported by Brandeis et al [14] from a national nursing home chain. They reported a 6-month healed rate of 39.9% for stage III ulcers and 34.1% for stage IV ulcers.

How does one account for the dramatic improvement in long-term outcome in the patients reported here versus those reported in the literature? One obvious reason is that the patients were closely observed by an interested team of wound care providers and had continual reinforcement regarding pressure relief and good skin and wound care. Another reason is that cytokine/growth factor therapy helps to place a chronic wound such as a pressure ulcer on a healing trajectory [19]. Although no differences were seen among the four treatment groups during the follow-up phase of the trial (Fig. 1), differences were seen during the active phase of treatment [1]. When patients receiving any cytokine therapy (GM-CSF, bFGF, or sequential GM-CSF/bFGF) were compared with those patients receiving placebo, significantly more patients treated with cytokines achieved >85% decrease in ulcer volume during the 35 days of active treatment ($P = 0.03$) [1]. The patients treated with bFGF alone did the best, having significantly more patients than the placebo group at >85% closure ($P = 0.02$) [1]. When one compared all patients who received bFGF (the bFGF alone group and the sequential GM-CSF group) with the placebo-treated patients, they healed significantly better than placebo-treated patients at >85% closure ($P = 0.02$) [1].

The growth factor response leading to >85% healing during the 35-day active treatment is important to the long-term outcome. This study shows that there is a significant improvement in the percent of patients healed at 1 year (84.6%) if >85% closure occurred during the 5 weeks of treatment compared with 61% if <85% healing occurred during the treatment phase (Fig. 4). Not only were there more patients eventually healed in that group, but they also healed significantly faster (Fig. 5). As only patients treated in one of the three growth factor groups reached ≥85% healing during the acute phase of the trial, it can be reasoned that the cytokine therapy resulted in the excellent long-term outcomes for the patients.

Acknowledgments

Supported by Grant R01-AR42967 from NIAMS, National Institutes of Health, Schering-Plough Research Institute and Scios, Inc., provided the cytokines used in this study.

References


