Decision Memo for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190N)

Decision Summary

CMS has determined that the evidence is adequate to conclude that autologous platelet-derived growth factor (PDGF) in a platelet poor plasma does not improve healing in chronic non-healing cutaneous wounds and, therefore, is not reasonable and necessary. CMS will continue noncoverage of this treatment.

CMS has determined, in the absence of specific evidence of benefit that there is not sufficient evidence to conclude that autologous platelet rich plasma is reasonable and necessary for the treatment of chronic non-healing cutaneous wounds. In light of the absence of data on the health outcomes of this treatment, we intend to issue a national noncoverage determination for use of this product except when used in accordance with the clinical trial policy defined in section 30-1 of the Coverage Issues Manual.

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Decision Memo

This decision memorandum does not constitute a national coverage determination (NCD). It states the intent of the Centers for Medicare & Medicaid Services (CMS) to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction, program memorandum, CMS ruling or Federal Register Notice, giving specific directions to our claims processing contractors. That issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.

To: Administrative File: (CAG-00190N)
Autologous Blood-Derived Products for Chronic Non-Healing Wounds

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Subject: Coverage Decision Memorandum for Autologous Blood-Derived Products for Chronic Non-Healing Wounds

Date: December 15, 2003

I. Decision

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CMS has determined, in the absence of specific evidence of benefit that there is not sufficient evidence to conclude that autologous platelet rich plasma is reasonable and necessary for the treatment of chronic non-healing cutaneous wounds. In light of the absence of data on the health outcomes of this treatment, we intend to issue a national noncoverage determination for use of this product except when used in accordance with the clinical trial policy defined in section 30-1 of the Coverage Issues Manual.

II. Background

A wound is a disruption of normal anatomic structure and function and can range from a simple scratch to an interruption that goes through tissue and muscle down to bone. Acute wounds are wounds of relatively new onset that heal in an orderly fashion, first by reestablishing epithelial integrity, then by laying down new collagen to strengthen the damaged tissue. The result is re-establishment of anatomic and functional integrity. Fortunately, most wounds are acute wounds that heal rapidly and uneventfully.

The process of wound healing involves an integrated series of cellular, physiologic, biochemical, and molecular events. The stages of wound healing are defined as inflammatory, proliferative, and remodeling. The inflammatory phase is characterized by platelet accumulation, coagulation, and leukocyte migration into the wound site. During this phase, the platelets adhere to collagen to form a vascular plug and the leukocytes, along with macrophages, begin removing cellular debris and bacteria. This inflammatory phase occurs during the first three to four days after a wound presents. The cellular interactions in this phase help to provide a temporary stable wound environment.

The proliferative phase, also termed fibroblastic, is characterized by regeneration of epidermis, angiogenesis, and the proliferation of fibroblast that forms collagen. Angiogenesis, the formation of a new vascular supply, is important for allowing the nutrition required in the healing process to invade the wound area. Type III collagen is produced during this phase and is instrumental in decreasing the wound size through contraction. The re-epithelialization helps to restore the cutaneous barrier. All of these physiologic events normally occur during the 10 to 14 day period after a wound presents.

The third and final phase of wound healing, the remodeling phase, takes place from a period of months up to 2 years.[1] This phase is characterized by collagen synthesis and degradation. The type III collagen produced during the proliferative phase is replaced by type I collagen. Continued wound contraction is also seen during this phase. Contractile forces are produced by contractile proteins that are present in the fibroblast of granulation tissue. At the end of remodeling, the resulting scar tissue is approximately only 80% the strength of normal skin[2].

The stages of wound healing are sequential in the normal healing process of acute wounds. Many chronic wounds fail to complete all the stages of normal wound healing.[3] When the healing process fails to progress properly and the wound persists for longer than one month, it may be described as a chronic wound. In chronic wounds, the healing process is disrupted by some underlying abnormality that prolongs the inflammatory phase, resulting in poor anatomic and functional outcome. Common underlying abnormalities include diabetes, abnormal external pressures and arterial, or venous circulatory insufficiency.

Since the etiology of wounds vary, the most effective therapy may vary as well. For example, the etiology of a pressure ulcer relates to unrelieved pressure on the skin, whereas the origin of a diabetic ulcer has other etiologies. Therefore, it is difficult to generalize the findings from studies on therapy from one type of ulcer to another type. According to the "Guidance for Industry-Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment," the Food and Drug Administration (FDA) states that "Wounds differ pathophysiologically, making it difficult-if not impossible-to generalize results obtained from a trial conducted in patients with one type of wound to those with another wound type. Separate safety and efficacy data should be submitted for each wound type for which an indication is sought."[4]

Wound care must be directed at providing an environment in which the body can effectively carry out the healing process. Conventional or standard therapy for chronic wounds involves local wound care as well as systemic measures. Standard care considerations to promote wound healing include debridement or removal of necrotic tissue, wound cleansing and dressings that promote a moist wound environment. Systemic treatments include the use of antibiotics to control infection and optimizing nutritional status. Early concepts in wound management involved soaking the wound in antiseptics to kill bacteria and then covering the wound with a dry dressing. As the biology of wound healing has become better understood, a variety of wound care strategies and products have been developed to help aid the healing process. Various new dressings such as alginates, hydrogels, films, and foam products are now used. Additionally, newer techniques such as negative pressure dressings, radiant heat, electrical stimulation and hyperbaric oxygen are also being investigated.

There are other conventional therapeutic modalities that may apply to certain subgroups of patients depending on their type of wound. Specific conventional therapies for venous ulcers include the use of compression devices aimed at decreasing venous stasis. Patients that have pressure ulcers require frequent repositioning to redistribute the pressure that is causing the ulcers. Good glucose control for diabetic foot ulcers and establishing adequate circulation for arterial ulcers are other ulcer-specific therapies.

The multitude of wound care regimens demonstrates the complexity of wound care management and the lack of one, universally proven treatment strategy. Knowledge of the pathophysiology of healing combined with realistic patient outcomes will help guide the clinician in choosing the wound care treatment plan. Lait and Smith reported that no single wound dressing is sufficient for all types of wounds and few are ideally suited for the treatment of a single wound through all phases of healing.[5]

Some wound care specialists have proposed that chronic wounds do not heal due to a lack of vital growth factors that are believed to be deficient in chronic wounds.[6] Several sources noted by Payne have proposed that this deficiency is due to repeated trauma, ischemia, and infection that increases the level of proinflammatory cytokines, increases the level of matrix metalloproteinases, decreases the presence of tissue inhibitors of metalloproteins, and lowers the level of growth factors.[7]

Originally, it was thought that platelets were important only for clot formation. However, it is now clear that platelets contain a large number of growth factors. The exact number and purpose of all of the growth factors is not known. Four growth factors are mostly frequently cited.[8] The first is the platelet derived angiogenesis factor that causes new capillary formation from the existing microvasculature.[9] Platelet-derived epidermal growth factor and platelet factor 4 (considered to be a chemoattractant for neutrophils) have also been identified. The fourth type is platelet-derived growth factor (PDGF), which is a potent fibroblast mitogen and chemoattractant.

With this knowledge, Dr. David L. Knighton developed, in 1985, a system to obtain multiple growth factors from platelets and started treating patients at the University of Minnesota. A retrospective study based on the first patients treated with PDGF was published in 1986.[10] The first prospective trial was then conducted by Knighton et al. and the results were published in 1990.[11] Dr. Knighton obtained a patent in 1992 on products released from platelets (i.e., platelet releasate) that are used for tissue repair. Procuren Solution® produced by CuraTech (which later became Curative Health Services) was available throughout the United States through 150 wound care centers starting in 1986. Marketing of Procuren Solution® ceased in 2001. However, various PDGF products, which contain multiple proteins like Procuren but do not contain cells like platelet rich plasma, are in use for patient care.

In 1997, FDA approved the biologics license application of Ortho-McNeil Johnson Pharmaceuticals, Inc. to market Regranex® (becaplermin) Gel 0.01%. The recombinant human platelet-derived growth factor-BB (rhPDGF-BB) was approved for the treatment of lower extremity diabetic neuropathic ulcers that extend into subcutaneous tissue or beyond and have an adequate blood supply. It was not approved for superficial ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers. Since becaplermin is not an autologous product, we have elected to not address this product in this decision memorandum.

In an attempt to improve the healing process, wound specialists have become more interested in autologous platelet rich plasma (PRP) produced by an apheresis process first developed by Charles Worden in 1998. In this process, autologous blood (blood donated by the patient) is centrifuged to produce a concentrate high in both platelets and plasma proteins. Individual growth factors are not identified or separated during this process. Additives are used to change the consistency of the product. Autologous PRP has been used for a variety of purposes such as an adhesive in plastic surgery and filler for acute wounds. It is also now being used on chronic wounds. PRP is different from earlier products in that it contains whole cells including white cells, red cells, plasma, platelets, fibrinogen, stem cells, macrophages, and fibroblasts and is used by physicians in a clinical or surgical setting. PDGF does not contain cells and was previously marketed as a product to be used by patients at home. Both PDGF and PRP gels are derived from the patient's own blood.

III. History of Medicare Coverage

CMS issued a national noncoverage determination for platelet-derived wound healing formulas in 1992. The decision was based in part on a review conducted by the Office of Health Technology Assessment in the Agency for Health Care Policy and Research dated July 1992 (AHCPR Pub. No. 92-0065).

CMS made a determination in April 2003, that autologous platelet rich plasmas were sufficiently different from PDGF to not fall under the 1992 national noncoverage determination. The differences noted in the CMS review were the inclusion of cells in the gel, the use by the provider versus at home use, and marketing as a process versus a product. As a result, questions regarding the efficacy of autologous PRPs have continued. On May 8, 2003, CMS began a national coverage determination process for autologous blood-derived products for chronic, cutaneous non-healing wounds.

Benefit Category Determination

For an item or service to be covered by the Medicare program, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act. There is no independent Medicare benefit category for autologous blood-derived products for treatment of chronic non-healing wounds. We have reviewed whether this treatment could be included as a component of a broader Medicare benefit category.

We believe that autologous blood-derived products application for the treatment of chronic non-healing wounds could be within the following benefit category:

1861(s)(1) Physician's service
1861(s)(2)(A) Incident to physician service

For autologous blood derived products application for the treatment of chronic non-healing wounds to be considered a physician's service 1861(s)(1) or "incident to physician service 1861(s)(2)(A)" under the Medicare program, it must be performed by or under the direct supervision of a physician.

IV. Timeline of Recent Activities

05/08/03 Opened NCD process based on requests received from Medicare contractors.

06/10/03 Meeting with Cytomedix to discuss their evolving technology.

06/17/03 Meeting with Medtronic to discuss their technology and recommendations.

07/10/03 Meeting with COBE to discuss technology and recommended wound treatments

08/11/03 Internal Technology Assessment completed.

V. FDA Status

At present, no blood-derived products are licensed and marketed for use in chronic non-healing wounds. FDA is considering the appropriate approval process for this technology. The potential exists that these products will not require FDA approval if produced for use in a clinical or surgical setting. The equipment used will need FDA approval. Currently, that equipment, in general, is approved for other indications. Therefore, this product can be marketed and used without any requirement to provide clinical data or development of its clinical effects.

VI. General Methodological Principles

When making national coverage decisions, we at CMS evaluate relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding of reasonable and necessary. The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Coverage Advisory Committee, evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve net health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.

- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study, or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome, and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied, and Medicare patients (age, sex, ethnicity, and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. The goal of our determination process is to assess net health outcomes, and we are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

CMS determines whether an intervention is reasonable and necessary by evaluating its risks and benefits. For all determinations, CMS evaluates whether reported benefits translate into improved net health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

VII. Evidence

A. Introduction:

The following summary represents the body of evidence for this decision. The evidence reviewed about the use of autologous, blood-derived wound healing products for chronic, non-healing cutaneous wounds includes the peer-reviewed literature evaluated by both external and internal technology assessment and external expert opinion.

It is important to note that Procuren is no longer commercially available. However, various platelet poor plasma products, which contain multiple proteins like Procuren but do not contain cells like platelet rich plasma, are in use for patient care.

The health outcome of interest to CMS in this decision memorandum is the impact of autologous, blood-derived wound healing products for chronic, non-healing wounds on the frequency of 100% epithelialization (i.e., complete wound healing). As noted by Payne,[12] long-term outcomes should be the desired outcome for wound care. He further noted that the Wound Healing Society has stated that acceptable healing must result in sustained anatomical and functional integrity, and that recurrence rates must be taken into account when considering the usefulness of wound therapy such as growth factors.

B. Discussion of evidence reviewed

1. The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: “Is the evidence sufficient to conclude that the application of the technology under study will improve final health outcomes for Medicare patients?”

The formulation of specific questions for the assessment recognizes that the effect of an intervention can depend substantially on how it is delivered, to whom it is applied, the alternatives with which it is being compared, and the delivery setting. In order to appraise the net health outcomes of autologous, blood-derived wound healing products for chronic, non-healing wounds in comparison with standard wound therapy and identify any relevant patient and facility selection criteria, CMS sought to address the following question:

Is there evidence of adequate methodological quality to conclude that the use of autologous, blood-derived wound healing products for chronic, non-healing wounds significantly and reliably improves 100% healing in the Medicare population?

2. External technology assessment

An external technology assessment was published by the Agency for Health Care Policy and Research Office of Health Technology Assessment in July 1992, titled "Procuren: A Platelet-Derived Wound Healing Formula."[13] They conducted a literature search and reviewed responses received from professionals involved with the study of growth factors. Only three published articles were found about platelet-derived wound healing formulas. Two were uncontrolled and the only controlled study was by Knighton in 1990.[14] For that article, the study quotes the author as saying "the study sample was small and randomization was not stratified according to diagnostic groups". They found that it was impossible to determine the clinical effectiveness of Procuren and suggested further research.

3. Internal technology assessment

We did a search on PubMed using the following terminology: Safeblood, Procuren, Autologel, growth factor, autologous, ulcer healing, wound healing, platelet derived, diabetic wound healing, wound treatments, ulcer treatments, blood derived, blood products, platelet grafting, autologous platelet rich plasma, wound care, and ulcer care. We did limit our search to articles that were in English and related to humans. We did not limit our search to recent articles (those published within the last 10 years) because we wanted to review the literature that was available when the current national coverage determination was made in 1992. In addition, we did not limit our search to studies conducted in the United States and/or studies using more advanced methodology as described in Section VI to assure that we obtained a broad understanding of the subject matter. The large number of articles identified for analysis was further narrowed by eliminating articles concerning homologous products, becaplermin, non-cutaneous (non-skin) use, and those articles not stating study results such as editorials. We also read all additional articles submitted as part of the public comment process.

Autologous platelet rich plasma

Numerous literature articles were submitted by external constituencies and a comprehensive literature search was conducted by CMS, but no evidence was found that focused on the use of platelet rich plasma in chronic, cutaneous non -healing wounds. CMS's review of the literature did locate articles with evidence on acute surgical wounds, such as coronary artery bypass grafting, maxillary sinus surgery, and facial reconstruction. However, the focus of many of these articles was on hemostasis of acute wounds and not specifically wound healing. In addition, as stated in our background section, acute surgical wounds sequentially complete all the stages of healing and, unless demonstrated otherwise by appropriate research, are assumed to respond differently to various therapies. Therefore, CMS did not include literature on acute wounds in our analysis.

Autologous platelet derived growth factors

As noted in Appendix 1, seven articles on platelet-derived growth factors were selected. Three of these articles, Glover, et al (1997), Knighton, et al (1989), and Margolis, et al (2001), were retrospective in nature and only one of these studies, Margolis, et al (2001), had any statistical weighting to control for the lack of a randomized design.

Glover, et al. (1997) reported a retrospective, uncontrolled, four-year study in wound care centers in 39 hospitals evaluating the effectiveness of platelet releasate for a variety of types of wounds. The frequency of 100% epithelialization was 65.7% and 50.8% in the treatment and control groups, respectively ($p<0.00001$).

Margolis, et al. (2001) reported a retrospective, controlled analysis of a subset of a large database to estimate the effectiveness of platelet releasate for diabetic ulcers. The investigators used regression analysis to develop a statistical control that would weight the results based on certain factors that could affect who might receive the platelet releasate treatment. The purpose of the statistical weighting of results was to control for the non-randomized nature of the retrospective study. The findings grouped patients into 5 groups by the probability of receiving the treatment. Of those who were included in the study, those most likely to receive the treatment had the most serious wounds. (Note that the highest grade wounds were excluded from the study.) The frequency of healing at 32 weeks (definition not provided in the article) was 50% and 41% in the treatment and comparison groups, respectively (statistically significant - $p < 0.001$).

Knighton, et al (1989B) conducted a retrospective, uncontrolled chart review of 20 diabetic patients. Eighteen of the 20 patients experienced 100% epithelialization.

One of the 7 articles, Knighton, et al (1986) was a prospective, case series of treatment in 41 patients with wounds of various etiologies. The mean time to 100% epithelialization was 10.6 ± 6.1 weeks.

The remaining three articles reported controlled, randomized studies. These articles, Knighton, et al (1990A), Krupski, et al (1991), and Stacey, et al (2000) are summarized below and discussed in our analysis of the evidence. All three clinical trials reported the frequency of 100% epithelialization as an outcome.

In Knighton, et al (1990A), 32 patients with at least 1 lower extremity wound of at least 8 weeks in duration were studied in a single center prospective, randomized, placebo-controlled, crossover, 2-arm trial. The type and extent of wounds were not restricted. Randomization was not stratified by wound type. Sixteen patients were randomized to active treatment with debridement plus daily PDGF releasate (dose not specified) for 12 hours followed by 12 hours of treatment with silver sulfadiazine. The remaining sixteen patients were randomized to debridement plus placebo every 12 hours. The patient applied the treatment. This part of the study lasted 8 weeks. After 8 weeks, all control patients were crossed-over to active treatment. Standard wound care was provided to all patients as needed. The mean age of the participants in the study was 64 years (standard deviation of 8 years) in the active treatment group and 62 years (standard deviation of 10 years) in the placebo group.

Patients were assessed every 2-3 weeks. The degree of epithelialization was determined visually at each visit. Wound dimensions were determined by direct measurement and photography. Wound area equaled the remaining unepithelialized wound surface. Wound duration was statistically significantly greater in the treatment group (119 ± 114 weeks) than in the control group (47 ± 63 weeks, $p=0.04$ (a clarification for a standard deviation greater than the mean was not provided in the article).

The frequency of 100% epithelialization at 8 weeks in the Knighton trial was 17/21 (81%) of wounds in the active treatment group and 2/13 (15%) of wounds in the control group. Intention to treat results and statistical analysis were not reported. The time to 100% epithelialization was 8.6 ± 4.2 weeks in the active treatment group and 15 ± 4.5 weeks in the control group ($p=0.002$).

Krupski, et al (1991) conducted a prospective, double-blinded, randomized, placebo-controlled, 2-arm trial. Stratified randomization by wound type was not performed. Wounds had to be greater than 8 weeks in duration and less than 100 cm^2 in area or less than 50,000 cm^3 in volume. Ten patients were randomized to debridement followed by active treatment with PDGF releasate (dose not specified) every 12 hours; 8 patients were randomized to a debridement plus normal saline placebo every 12 hours. The patient applied the treatment. Standard wound care was provided to all patients as needed.

Patients were assessed every week. Wound dimensions were determined by directly measuring length and width and then calculating the surface area and volume. Photography was used to validate the direct measurements. Rate of healing was the primary outcome and was determined by calculating the differences between initial and final wound areas and volumes and dividing this figure by the number of weeks of therapy. A healed wound was defined as a wound visually determined to be completely covered with new epithelium. The frequency of 100% epithelialization at 12 weeks was also determined.

A total of 26 wounds were treated; 17 with PDGF and the remaining with placebo. Twenty-eight percent of the patients had venous insufficiency, 72% had occlusive peripheral vascular disease, and 78% had diabetes. There were no statistically significant differences in distribution of wound types or any other patient variable between active treatment and control groups. Mean age in the active treatment group was 66 ± 5 years and 67 ± 4.5 years in the control group.

The frequency of 100% epithelialization at 12 weeks was 4/17 wounds (24%) in the active treatment group and 3/9 wounds (33%) in the control group (p= NS). The healing rate by surface area was –4.3 ± 12.2 cm2/week and 1.9 ± 2.7 cm2/week in the active treatment and control groups, respectively (p= NS). The healing rate by volume was –0.1 ± 0.7 cm3/week and 0.1 ± 0.2 cm3/week in the active treatment and control groups, respectively (p= NS). Hence, while the wound minimally decreased in size in the control group, the wound actually increased in size in the treatment group.

In Stacey, et al (2000), 86 patients with wounds due to venous insufficiency were studied in a prospective, double-blinded, randomized, placebo-controlled, 2-arm trial. The duration and extent of wounds were not specified. Forty-two patients were randomized to active treatment with twice weekly PDGF lysate (dose not specified). Forty-four patients were randomized to twice weekly placebo. Treatment was applied by a clinician in a wound clinic until the wound healed or for no more than 9 months. Number of wounds and the specifics of standard of care were not reported.

Patients were assessed every week. Wound dimensions were determined by direct measurement, photography, and planimetry (details not provided). Wound healing over 9 months was the primary outcome (details not provided).

Mean age was 72 years (range of 35-90) in the active treatment group and 70 years (range 26-92) in the placebo group. Wound healing over 9 months occurred in 33/42 (79%) and 34/44 (77%) of patients in the treatment group and control group, respectively (p= NS).

4. MCAC

This issue was not referred to MCAC.

5. Evidence-based guidelines

Four guidelines pertaining to growth factors were identified in our review.

- Diabetic foot disorders: a clinical practice guideline (2000) developed by the American College of Foot and Ankle surgeons recommends the use of becaplermin (a non-autologous growth factor) but does not specify the type of evidence used to support these guidelines.
- The guidelines developed by the Wound, Ostomy, and Continence Nurses Society, Guideline for management of wounds in patients with lower-extremity arterial disease (2002), recommends considering the use of platelet rich plasma with a level B of evidence. Level B evidence is when one or more supporting controlled trials on lower extremity arterial disease in humans exist or two or more supporting trials in an animal model exist.
- Pressure ulcer therapy companion (1999) developed by the American Medical Directors Association notes that regenerative growth factors have been helpful for some chronic non-healing wounds but FDA approval is still pending for pressure ulcers. The majority of recommendations in these guidelines are based on expert opinion.
- The guidelines developed by the Agency for Healthcare Research and Quality (a Federal Government Agency, Treatment of pressure ulcers (1994 and reviewed in 2000) notes, "The therapeutic efficacy of miscellaneous topical agents (e.g., sugar, vitamins, elements, hormones, other agents), growth factors, and skin equivalents has not yet been sufficiently established to warrant recommendation of these agents at this time (strength of evidence = C.)" Level C evidence requires one of the following: (1) results of one controlled trial; (2) results of at least two case series/descriptive studies on pressure ulcers in humans; or (3) expert opinion.

6. Professional Society Position Statements

We were not provided nor were we able to identify any professional society position papers.

7. Expert Opinion

Six companies contacted CMS. Upon request, CMS met with three of these companies after the national coverage determination process was started (Cytomedix, Medtronic, and COBE) to discuss the current state of wound healing with autologous, blood-derived wound care products for chronic, non-healing wounds. The remaining three companies, Harvest Technologies Corporation, Safeblood Technologies, and Innovative Medical Technologies, submitted information for CMS review. We also received comments from some individual providers. Generally, they were all supportive of the promise of the product and procedure. However, two of the companies, Cytomedix and Medtronic, cautioned CMS that they did not believe sufficient evidence was available for CMS to make a decision and informed us they were planning on conducting trials using autologous platelet rich plasmas. Safeblood technologies submitted a position statement, an overview of the Safeblood procedure, and an unpublished report of a retrospective case series written by RA Dellinger, DPM. The documents were assessed as lower quality evidence with significant potential bias and confounding, using the critreia in Section VI of this document.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under section 1869(f)(1)(B) of the Social Security Act (the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member” (section 1862(a)(1)(A) of the Act).

a. Platelet rich plasma

We were unable to locate any clinical studies evaluating the use of platelet rich plasma in chronic, nonhealing wounds. All literature found only addressed the use of platelet rich plasma in acute wounds and, as discussed above, it frequently was investigating hemostasis and not wound healing. We also considered the potential of generalizing the evidence from PDGF to PRP. Even if generalization was possible, the evidence for PDGF is negative and would not support a benefit for PRP. However, as we previously stated, we believe that the products are distinct, which precludes generalizing from one therapy to the other.

Therefore, we conclude that the evidence is not sufficient to conclude that the use of platelet rich plasma improves outcomes in patients with chronic, nonhealing, cutaneous wound and is therefore not reasonable and necessary. For that reason, we will issue a noncoverage determination for this indication.

b. Autologous, Platelet-derived growth factors (PDGF)

The vast majority of the literature contains retrospective studies that were uncontrolled. Retrospective studies submitted and identified during the literature review suffered from the limitations noted in Section VI of this decision memorandum. Therefore, the results of these studies were considered to be unreliable and were given limited weight in our decision. While the trial design in Knighton, et al (1986) article was a prospective case series, it was not randomized and a control was not used.

Three controlled studies were identified and included in the analysis. All three studies reported the frequency of 100% epithelialization as an outcome. Two of these studies, Stacey, et al (2000) and Krupski, et al (1999), did not find PDGF to be effective in chronic, nonhealing cutaneous wounds. The remaining study, Knighton, et al (1990), did show a benefit to treatment with PDGF but had major methodological deficiencies as noted below.

The controlled study by Stacey et al (2000) did not demonstrate that PDGF improved the frequency of healing compared to placebo in patients with venous insufficiency. Each arm showed a similar, and high, healing rate (79% for PDGF and 77% for placebo) over 9 months.

The strength of this study was in its randomization and clear end point of complete healing. Its major weaknesses included a lack of information as to the duration and extent of wounds to determine the comparability of the two groups and the lack of a clear definition of standard wound therapy applied to each patient.

The Krupski, et al (1991) study did not show that treatment with PDGF was better than placebo with regards to frequency of 100% epithelialization. In fact, the control group had a greater frequency of 100% epithelialization than the active treatment group. Though a prospective, randomized study, the sample size of 18 patients with 27 wounds is inadequate to draw conclusions from the results.

The Knighton, et al (1990) study was a controlled trial that showed a statistically significant clinical outcome, time to 100% epithelialization, when using PDGF in patients with chronic, cutaneous nonhealing wounds. The frequency of 100% epithelialization at 8 weeks was 17/21 (81%) of wounds in the active treatment group and 2/13 (15%) of wounds in the control group. However, the results of statistical analysis were not reported; perhaps because this outcome was not the prospectively defined primary outcome.

This study suffered from a number of deficiencies including ambiguity about the use of blinding and the lack of stratification of randomization by wound type. The prospectively defined sample size was small and was made worse by the exclusion of 8 patients (3 in the active treatment group and 5 in the control group) for various reasons. Also, the use of silver sulfadiazine in only the active treatment arm was a significant confounder in the assessment of the benefit of PDGF.

In summary, the better-designed trials show no benefit of PDGF over standard care and the remainder of the trials have significant design flaws that do not allow any level of confidence that the results reflect the true effects of the intervention. Therefore, CMS concludes that the evidence is sufficient to demonstrate that PDGF does not improve outcomes in patients with chronic, nonhealing cutaneous wounds. For that reason, CMS concludes that PDGF is not reasonable and necessary and the current noncoverage determination will remain in effect.

CMS does provide for an exception to its noncoverage policy in the Clinical Trial Policy (Coverage Issues Manual 30-1) to promote clinical trials. We were able to view protocols being developed by two companies in preparation for the approval process at FDA and encourage these trials to move forward. Therefore, in accordance with CIM 30-1, CMS will provide reimbursement for the routine costs in Federally-sponsored or approved clinical trials assessing the efficacy of platelet rich plasma in treating chronic non-healing cutaneous wounds.

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