



Original Contribution • 2001 BSN Medical Call for Papers - 3rd Place

Apligraf: A Promising New Wound Care Treatment for the 21st Century

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CHRONIC WOUNDS

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smoking, injury, limited joint mobility and susceptibility to infection.

VENOUS ULCERS

Venous leg ulcers are caused by venous insufficiency or poorly functioning valves in the veins of the legs. Chronic venous insufficiency affects about 7 million people in the United States. Older adults are more prone to developing venous ulcers, and this number is expected to rise greatly as the baby boomer generation ages.

The valves in the veins of the legs send blood flow from the capillary beds to the superficial system and then to the deep venous system. When these valves don't function properly, venous hypertension in the superficial veins occurs. Chronic localized venous hypertension leads to surrounding tissue damage, which untreated can lead to venous ulceration. To reduce the risk of developing a venous leg ulcer, patients should be educated to proper nutrition and exercise, avoid long periods of sitting or standing, no smoking, wear support stockings, and inspect legs and feet regularly for signs of infection or injury.

Symptoms of venous ulcers can include redness, leg swelling, pruritis, scaling, discharge and eczematous changes with brown pigmentation in the lower extremity. These ulcers typically develop on the medial aspect, possess irregular borders and may contain a bacterial infection. Pain is also often present sometimes severe when combined with an infection.

APLIGRAF

Standard care for these chronic ulcers may not heal wounds fast enough to avoid life-threatening infections that lead to amputation. Finding a method that will stimulate rapid healing decreases the chance for amputation. Apligraf should be one of those methods considered.

Apligraf was first approved by the FDA in May 1998 for the treatment of venous ulcers greater than one month in duration that have not responded to conventional ulcer therapy. After this success and more trials, on June 20, 2000 the FDA approved Apligraf for the treatment of neuropathic diabetic foot ulcers greater than 3 weeks in duration that have not responded to standard compression therapy.

Apligraf is a bi-layered living skin substitute with an appearance and feeling of human skin. This tissue-engineered product is produced from normally dis-

carded newborn human foreskin and a type I bovine derived collagen. Cells from these are cultured, expanded and transferred to working cell banks where they are multiplied and frozen. The infant donor and his mother's cells are tested extensively to prevent any infectious agents. The need for donors is very low because just a single donor foreskin can provide enough skin substitute to cover the equivalent of a football field.

Apligraf contains all the growth factors normally found in human skin. It has both an epidermis and dermis with living keratinocytes and fibroblasts. However, it does not contain Langerhans' cells, melanocytes, white blood cells, blood vessels, hair follicles or sweat glands. The absence of these may explain why it has such tolerance and no clinical evidence of rejection on any patient tested to date. It also does not show changes in blood work or any other serious adverse effects.

Apligraf was developed and manufactured by Organogenesis Inc., of Canton, Massachusetts and marketed by the Novartis Pharmaceutical Corporation. It takes approximately 20 days to produce the Apligraf from the time when the human cells are taken from the cell bank to when they are ready to be shipped. It is produced in a circular disk about 75 mm or 3 inches in diameter and 0.75mm thick. It is packaged in a sealed heavy-gauge polyethylene bag with 10% CO₂ air atmosphere and a nutrient medium. It is usually shipped overnight depending on the date scheduled for patient application. When it is received, it should be kept in the sealed bag at room temperature between 68-88 degrees Fahrenheit. It has a maximum shelf life of 5 days from the day of packaging.

PREPARATION

Preparation of the ulcer is very important in achieving success of the Apligraf. Along with standard wound care, some physicians choose to use a topical medication such as Regranex for 1 month prior to application. This is to create a granular wound which is found to be much more effective in achieving complete skin closure when using the Apligraf. There are over 4,000 wound care medications on the market today but a physician must be aware of how they may interact with the Apligraf before using.

One week prior, the Apligraf is ordered, aggressive wound debridement of necrotic tissue is per-

formed, and the physician may order a course of systemic broad-spectrum antibiotics to be sure there is no risk of underlying infection. Some physicians may also suggest having the patient apply silvadene cream to the ulcer two days prior to application, decreasing the chance of any bacterial contamination before grafting.

APPLICATION

On the day of application, the ulcer is again debrided and rinsed thoroughly with sterile saline. The Apligraf is carefully removed from the circular disk by hand or blunt forceps and placed on a saline moistened 4x4 gauze. The dull epidermal side, face down and shiny dermal side, face up on the gauze. It is then perforated or fenestrated using a sterile scalpel or scissors about one slit per centimeter. This allows fluid to drain which aids in adherence to the wound bed. Then the Apligraf is applied to the wound so that the shiny dermal side is in contact with the ulcer bed. A slight overlap of 0.5cm on the ulcer edge can help encourage better adherence and stimulate the epidermis of the wound edge. Air pockets should be eliminated while smoothing out the Apligraf with a sterile cotton tipped applicator.

This area is then covered with a non-adherent dressing such as Adaptic or Xeroform, along with a secure pressure bolster or folded gauze, compressing the graft directly upon the underlying bed, then wrapping securely with a roll of Kerlix gauze. Its important to be wrapped properly so no slippage occurs. An elastic compression bandage is then used for more stability. It is not necessary to anchor this by sutures or staples.

However, this can be performed if the physician desires, but this would mean the need for a local anesthetic. A secure compression bandage along with proper unloading has usually been found sufficient. Options to offload diabetic patients may be crutches, wheelchair, posterior splint, removable cam walker boot, Ipos or Darco wedge shoe or even a short leg cast. This may depend greatly on the location of the ulcer and compliance of the patient. For patients receiving the Apligraf for venous leg ulcers it is always recommended to use compression therapy in conjunction with the Apligraf.

POSTAPPLICATION

Dressing changes should occur 3 to 5 days after application and then once a week after that. Great care

is required when removing the dressing. Saline moistened gauze may be needed to loosen any dressing adhering to the wound. Being very careful to avoid pulling the Apligraf away. The graftskin may appear transparent and dull. It can have a mild smell with greenish or yellow gelatin substance. It is important to be able to differentiate correctly the normal appearances of the Apligraf versus those signs of an actual infection. No debridement should be performed. The average time for a complete wound closure when using the Apligraf for diabetic foot ulcers is 65 days vs 90 days using standard wound care only.

Reapplication may be necessary if there is an area that does not adhere, however this should not be considered any earlier that 6 weeks after the 1st application. A 2nd graft may be beneficial but not much data supports any more improvement when 3 or more grafts are used. An average number of 1.41 applications are required for ulcers to completely close.

CONTRAINDICATIONS

The only real risk of using the Apligraf is an incomplete graft. The problems of an incomplete graft may be due to wound infections, inadequate debridement, extended duration of an ulcer, or poor application technique by the physician. It should not be applied to patients with a known bovine allergy. Noncompliance of patients is also a factor when using the Apligraf as it is in a majority of any chronic wound care. Apligraf has been found to be a significant improvement over standard treatment for venous leg ulcers and diabetic foot ulcers.

Previously, when standard treatments did not respond, skin grafting was an alternative. Now an advantage of the Apligraf is that unlike skin grafting no donor site is needed. Harvesting donor sites were often painful and slow to heal. It also put the patient at risk for an infection, scarring, alteration of skin pigmentation and possibly the need for additional grafts. Apligraf eliminates the need for anesthesia and is performed without any pain to the patient. It is safe, well tolerated, reliable, noninvasive, a low incidence of adverse reactions, and non-traumatic for patients.

COST

The care of chronic wounds is very expensive with an estimated cost of over \$1 billion dollars a year in the United States. This is a significant amount of money spent each year on caring for these patients. High costs can be related to hospitalization, surgery, rehabilitation, home healthcare, supplies, nursing home care, loss of work and wages. Chronic wounds are also very time consuming in their care and healing because of reoccurrence. Most patients who develop a lower extremity ulcer are more likely to develop another one on the other extremity within 2 years of their first diagnosis.

Chronic ulcers progress to amputation in 84% of people and half of those are usually diabetics. An amputation does not put an end to the cost of caring for these patients. Failed vascular reconstruction, long term rehabilitation and possible loss of productivity in society should all be considered in final cost analysis. These costs can range from \$20,000 to \$60,000 per patient. They also have an increased risk for further amputation. Another concern is the high morbidity rate in diabetic patients, who have been preceded by an amputation. It is felt that the Apligraf could help decrease those numbers greatly by accelerating healing time leaving less risk of wound infection.

Currently the cost of the Apligraf is about \$1000 to your facility. Apligraf qualifies for reimbursement by Medicare when applied in the hospital out patient setting or the physicians office. The federal Health Care Financing Administration (HCFA) provides a clear national standard for the level of reimbursement. Physicians can submit for the material of the Apligraf, cost of their services, and the application procedure.

Coverage includes the Apligraf under the HCPCS code C1305. The application procedure can include CPT code 15000 for preparation of the wound bed, 15342 and 15343 for applying the skin substitute depending on whether one or more pieces are needed. Total cost of applying the Apligraf in the physicians office will be less than \$2500. Insurance companies are seeing this as a very cost effective treatment and many have followed Medicare in their coverage of this product. Novartis also has an Apligraf reimbursement hotline and support center available to answer any questions regarding medical necessity, billing codes and reimbursement to your facility.

CONCLUSION

In the 21st century we will see many advances in bioengineered products to improve patients quality of life. The FDA stated that "although Apligraf will not eliminate the need for standard treatment its use may enhance and shorten the healing process. Its special composition allows it to provide wound protection and to foster the growth of healthy new skin."

At this time, approved useages for the Apligraf is limited to venous leg ulcers and diabetic foot ulcers but further testing and experimentations are being done to investigate other possible ways to use the Apligraf such as pressure ulcers, burns, skin cancers, surgical excisions and donor sites.

Whether Apligraf is the cure for ALL chronic wound patients remains to be seen, however, it is a promising new wound care treatment that could provide great benefit. The benefits to potentially heal wounds faster reduces the possibility of infection, amputation, and hopefully death. Apligraf should ALWAYS be considered as a treatment option for those patients with chronic hard-to-heal venous leg ulcers and diabetic foot ulcers.

ABOUT THE AUTHOR

Robyn Masseth, OTC,CMA, has been employed in Orthopedics and Podiatry by Meritcare Health System in Fargo, North Dakota for the past 15 years. She has been a member of NAOT since 1994 and attends the annual NAOT symposium each year. Robyn loves teaching and learning all she can about Orthopedics.

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