



Taking a Fresh Look at Regranex Gel

This advanced tissue product is an important wound healing supplement.

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Regranex (Becaplermin) gel 0.01% is an FDA-approved, advanced wound-healing pharmaceutical drug containing a recombinant form of human platelet-derived growth factor. While widely popular when first developed, it is now often overlooked due to newer advanced regenerative tissue therapies that have since been developed. However, Regranex gel is proven to be successful in assisting wound closure and should be considered as an option along with newer regenerative tissue products when treating diabetic neuropathic foot ulcerations.

Regranex gel contains platelet-derived growth factor (PDGF) to assist in wound-healing. PDGF is one of the most widely studied proteins found in the body, and it plays significant roles in cell growth and division. In the body, when tissue damage occurs, platelets release PDGF in response to start the healing cascade. PDGF promotes the chemotaxis, or migration, of immune cells such as neutrophils and macrophages to clean and clear the area of debris. These newly recruited cells also release their own PDGF that further recruits cells to accelerate this cascade. Once a clean environment has been achieved, PDGF continues to work, promoting chemotaxis of fibroblasts and smooth muscle cells that upon arrival begin building reparative structures.

Fibroblasts play the role of pro-

ducing connective tissue, secreting collagen to create the framework. Smooth muscle cells that have been called for by PDGF mediate the process of angiogenesis. Even after initial scar tissue has been laid down, a vascular network has been created and damage may appear healed on the surface, and PDGF is still at work deep orchestrating further cellular activity to remodel and mature these tissues.

Given the vast and important

response, healing stalls and wounds become chronic in nature.

With so many wound care products available and many new products coming to the market, it is often difficult to sort through each product, determine its use and cost-effectiveness and decide how a product will fit into one's practice. Wound healing took an exciting turn after regenerative tissue products became available. Grafts made from the tissues of animals, cultured human cells, and

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roles of PDGF, Regranex gel was created to supplement this cycle in diabetic neuropathic foot ulcerations. Individuals with diabetes mellitus may often be malnourished, lacking the essential proteins, minerals, and vitamins in their diet to produce the necessary cells and signaling proteins to allow for normal cellular function and immune response. In addition, glycation of these cellular proteins in the body due to abnormally elevated blood glucose levels found in individuals with diabetes mellitus leads to immune cell deformation and the inability of receptor-mediated responses which may further degrade the already limited response to wound healing. Without the appropriate re-

even donated amniotic tissues from the birthing process have offered hope in achieving healing in chronic diabetic ulcerations. However, these products are expensive to produce and manufacture; unlimited application of these products to any wound is unreasonable.

Advanced tissue products should typically only be utilized if a wound is present for four continuous weeks, had been treated under the guidance of a medical professional, and had not achieved at least 50% healing over that time period. This protocol is based on research showing that wounds that did not obtain 50% healing at the four-week mark were significantly

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less likely to heal than wounds that did achieve 50% healing in the time frame.¹ However, while evidence-based medicine should be the cornerstone of medical care, the knowledge and expertise of clinicians should not be overlooked. While

never 100% accurate, most clinicians treating wounds in their practice get a sense of which wounds are going to be difficult to heal. Furthermore, when we see an established patient whom we previously treated with difficult-to-heal wounds return with a new wound, we may be confident that this new wound will be no different. To the treating provider and the patient alike, waiting four weeks may seem like an eternity when the stakes are high. Open wounds are portals for infections that lead to limb loss in our most compromised patients. In these cases, we desire to do anything and everything possible from the start. This is where Regranex gel may be the most exciting. Regranex gel is FDA-approved to be applied at the onset of any diabetic neuropathic foot ulceration that extends into the subcutaneous tissue layers as long as adequate blood supply is available.²

As already explored, PDGF plays a significant role in wound healing, and applications of Regranex gel may have significant impact on wound healing. Studies were done on this product when it first arrived many years ago, and results showed much promise. In 1999, the results of a combined analysis of four multicenter, randomized, parallel group studies were presented by Smiell and colleagues.³ 874 patients with a wound of $\leq 10\text{cm}^2$ were included in determining efficacy of Regranex gel compared to a placebo gel. The results showed a significant increase in wound healing, with 50% of the wounds obtaining closure with the use of Regranex (100 $\mu\text{g/g}$ bclaplermin) gel compared to only 36% with the placebo group. Embil and colleagues⁴ revealed the results of their open-label study in 2000, finding

than other regenerative tissue products. Regranex gel is applied daily to the wound, allowing for consistent influx of PDGF to provide continual activation of the wound-healing cycle. When this critical growth factor is delivered to the wound sooner, faster wound-healing may be seen as demonstrated by the aforementioned studies. Furthermore, daily dressing changes allow for the wound to be visualized regularly to ensure no signs of infection develop, an advantage over a secured tissue graft which may cover and obstruct a good view of the wound bed. Regranex may be used in adjunct with other advanced products as well. It may be used in the first weeks of wound

care to prepare the wound bed by increasing granulation tissue before the use of a regenerative tissue graft, thus potentially improving the overall ef-

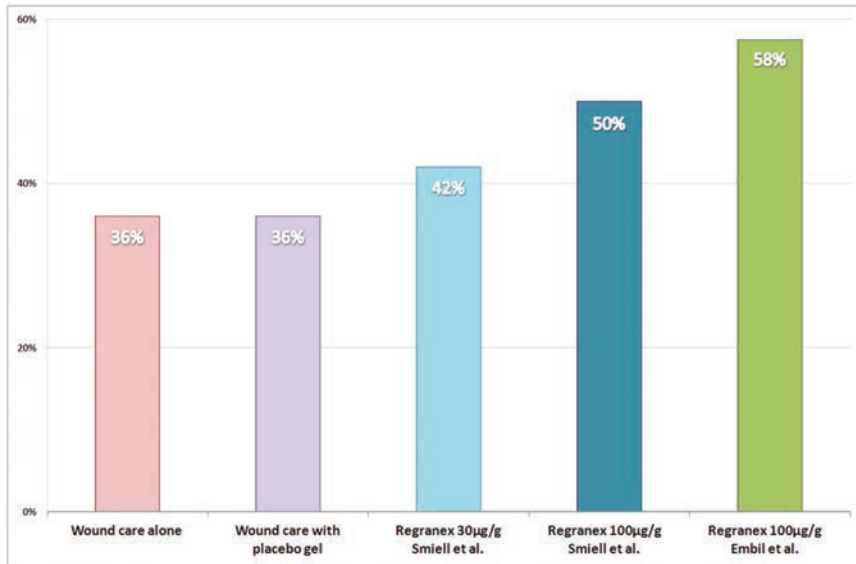


Chart 1: Estimated rate of complete healing in the combined analysis of Smiell and colleagues as well as inclusion of rate of closure in the open label study by Embil and colleagues.

that 57.5% of their 134 patients who utilized Regranex gel had complete closure. Both studies by Smiell et al. and Embil et al. performed once-daily

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dressing changes with Regranex (100 $\mu\text{g/g}$ bclaplermin) gel and recorded similar results with approximately half of their patients achieving closure as compared to only about a third in the control group found in the large randomized study by Smiell and colleagues (Chart 1).

Regranex gel offers advantages and may prove very useful in some patients. As previously mentioned, Regranex gel can be utilized early in the appearance of diabetic neuropathic foot ulceration. Regranex is considered a pharmaceutical medication and oftentimes costs significantly less

efficacy to achieving closure. Regranex gel may also be used in later stages of wound-healing when wound-healing has become slow or even stalled, which may help restart the inflammatory cascade induced by PDGF.

Case One

Case one is a 54 year old female with diabetes mellitus type 2 complicated by end stage renal failure and severe peripheral arterial disease. She was admitted to the hospital due to a necrotizing infection of the left foot, which resulted in an above the knee

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amputation due to her severe PAD. Shortly after undergoing the left-sided amputation, her limited activity due to the inability to walk, the need for bed rest and underlying peripheral neuropathy resulted in the formation of an ulcer on the right posterior heel. Proper off-loading techniques and wound cares were initiated and non-invasive vascular studies were performed to ensure adequate vascular flow. The initial ulceration measured 3.8 x 2.8 cm (Figure 1). It was decided to use Regranex gel at the onset to allow for advanced therapy as soon as possible due to the

healing concerns in this patient with a complicated medical history. Regranex gel was used for two months with daily dressing changes in this individual and the wound decreased in size to 2.6 x 1.4 cm with a resultant healthy, granular bed (Figure 2). The granular bed produced was ideal for receiving a bioengineered regenerative tissue graft which was the next step for this patient.



Figure 1: Initial 3.8 x 2.8 cm full thickness ulceration at the right posterior heel of a 54 year old female with diabetes mellitus type 2 and end stage renal disease.



Figure 2: Wound reduction from 3.8 x 2.8 cm to 2.6 x 1.4 cm after two months of daily Regranex applications. Wound now ready to accept a bioengineered regenerative tissue graft.



Figure 3: Large full thickness ulceration measuring 5.7 x 1.8 cm of the right lateral foot in a 50 year old male patient with diabetes mellitus type 2 and acquired immunodeficiency syndrome (AIDS) resulting after resection of osteomyelitis in the foot and placement of negative pressure.



Figure 4: Complete healing of previous right lateral foot ulceration after 3 months of daily treatments with Regranex gel.

Case Two

Case number two is a 50 year old male with diabetes mellitus type 2, acquired immune deficiency syndrome and history of venous insufficiency of the lower extremities. This patient underwent surgical resection of the right 5th metatarsal and associated digit due to osteomyelitis and active infection caused by a previous diabetic neuropathic ulceration.

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Figure 5: A chronic, non-healing ulceration measuring 3.6 x 1.9 cm with no change in size over a 2 month span located on the posterior aspect of left calf as the result of trauma in a 64 year old female patient with diabetes mellitus type 2.



Figure 6: After starting once daily applications of Regranex gel wound healing restarted and the wound closed after 3 months.



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After surgical resection was completed, antibiotics and negative pressure were utilized until any signs of infection were resolved. The resultant wound on the right lateral foot was 5.7 x 1.8 cm (Figure 3). Regranex gel was initiated at this point along with daily dressing changes to expedite healing. Healing was obtained in this patient three months later, using only Regranex gel with daily dressing changes (Figure 4).

Case Three

Case number three is a 64 year old female with diabetes mellitus type 2 who was involved in a motor vehicle accident which resulted in a large traumatic wound of the left posterior calf measured at 7.8 x 5.5 cm post-debridement. This individual had a complex medical history involving chronic leg edema with resultant lymphedema changes and allergies to many medications, materials, and textiles which

dramatically limited options for wound care. Standard wound cares with compression were initiated to the left leg. This resulted in slow, but continuous, wound healing which occurred over the course of five months until the wound reached margins of 3.6 x 1.9 cm (Figure 5). The wound-healing then slowed, and limited improvement occurred over the next month until there was complete stalling and lack of any improvement of the wound for the next two months. Once a day application of Regranex gel was initiated at this point, with twice daily dressing changes. Over the course of the next three months, wound healing restarted and complete closure of the wound was achieved (Figure 6). **PM**

References

¹ Sheehan, et al. Percent Change in Wound Area of Diabetic Foot Ulcers Over a 4-Week Period Is a Robust Predictor of Complete Healing in a 12-Week Prospective Trial. *Diabetes Care*. 2003. Jun;26(6):1879-82.

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² Regranex Prescribing Information. http://www.regranex.com/pdf/PI_Full_Version.pdf. Sept 2012.

³ Smiell, et al. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair Regen*. 1999. Sep-Oct;7(5):335-46.

⁴ Embil, et al. Recombinant human platelet-derived growth factor-BB (becaplermin) for healing chronic lower extremity diabetic ulcers: an open-label clinical evaluation of efficacy. *Wound Repair Regen*. 2000. May-Jun;8(3):162-8.



Dr. Johnson recently signed on to be a staff surgical podiatrist at Sanford Health in Bemidji, MN where he now treats patients at the newly constructed Sanford Bemidji Wound Care & Hyperbaric Center.